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UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Alexander KOZAK, et al.
	Serial No.:	To Be Assigned
	Filed:	Simultaneously Herewith
	For:	**Phospholipid Derivatives of Non-Steroidal Anti-Inflammatory Drugs**

Assistant Commissioner for Patents
Washington, D.C. 20231
BOX: PCT

May 16, 2001

LETTER RE: PRIORITY

Sir:

Applicants hereby claims priority from Israeli Patent Application No. 127143 filed November 19, 1998 through International Application Serial No. PCT/IL99/00623 filed November 18, 1999.

Respectfully submitted,
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BY: _____

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PRIORITY DOCUMENT

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This 23 -11- 1999 היום

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נתאשר

Application for Patent

תאריך Date הוקדם/נדחה Ante/Post-dated
19 -11- 1998

י, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
(Name and address of applicant, and in case of body corporate-place of incorporatio

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Inventors: Alex Kozak
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ממציאים: אלכס קוזאק
ישראל שפירו

בעל אמצאה מכח החוק
Owner, by virtue o

ששמה הוא Low
of an invention the title of which is

נגזרות פוספוליפידיות של תרופות אנטי-דלקתיות שאינן סטרואידיים

PHOSPHOLIPID DERIVATIVES OF NON-STEROIDAL ANTI INFLAMMATORY DRUGS

hereby apply for a patent to be granted to me in respect thereof.

בקש בזאת כי ינתן לי עליה פטנט

*בקשת חלוקה - Application of Division	*בקשת פטנט מוסף - Application for Patent Addition	*דרישה דין קדימה Priority Claim		
מבקשת פטנט from Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האגוד Convention Country
מס'/No.	מס'/No.			
מיום/dated	מיום/dated			
* יפוי כח: מיוחד - רצוף בזה / עוד יוגש P.O.A.: general / individual-attached / to be filed later -				
הוגש בעניין/filed in case				
המען למסירת מסמכים בישראל Address for Service in Israel **תיקנו DPL/010** Dr. Cynthia Webb P.O. BOX 2189 Rehovot, 76127				
חתימת המבקש Signature of Applicant For the Applicants, Dr. Cynthia Webb Patent Attorney		* היום .....18..... בחודש ...נובמבר..... שנת 1998... This 18 day of November, 1998		
		לשימוש הלשכה For Office Use		

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DPL/010

PHOSPHOLIPID DERIVATIVES OF NON-STEROIDAL ANTI INFLAMMATORY DRUGS

נגזרות פוספוליפידיות של תרופות אנטי-דלקתיות שאינן סטרואידים

D-PHARM Ltd.
Inventors: Alex Kozak
Israel Shapiro

די פארם בע"מ
הממציאים: קוזאק אלכס
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PHOSPHOLIPID DERIVATIVES OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

FIELD OF THE INVENTION

The present invention relates to compounds comprising non-steroidal anti-inflammatory drugs (NSAID) covalently linked to a phospholipid moiety via a bridging group, to pharmaceutical compositions comprising such compounds and to the use thereof for the treatment of diseases and disorders related to inflammatory conditions. The invention further relates to a process for the synthesis of said phospholipid derivatives of NSAIDs.

BACKGROUND OF THE INVENTION

Inflammation is an important aspect of the natural defense process. Inflammation becomes a pathological process, requiring medical intervention, when inflammatory mediators cause excessive damage to the surrounding tissue. Examples of such pathological processes are rheumatoid arthritis (RA) and psoriasis. Recently, a significant inflammatory component has been found in other types of disease, for example, neurological disorders such as multiple sclerosis and Alzheimer's disease. A common feature of many inflammatory diseases is an elevation in phospholipase A_2 (PLA_2) activity.

PLA_2 is the common name for a diverse group of enzymes that specifically hydrolyze the sn-2 bond of glycerophospholipid to release free fatty acids and lysophospholipids. PLA_2 is thought to be rate limiting in the release of arachidonic acid. The other product of its reaction, lysophospholipid, is thought to be the precursor of platelet activating factor (PAF). PAF and the arachidonic acid metabolites, eicosanoids, are pro-inflammatory lipid intermediates derived from mobilized cell membrane phospholipids by the action of phospholipase enzymes. PLA_2 is thus implicated as having a crucial

role in the production of the entire cascade of phospholipid–derived inflammatory mediators.

For persistent inflammation three classes of drugs are widely used, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and slow acting disease modifying drugs.

Corticosteroids are the most potent and effective agents in controlling inflammatory conditions. Unfortunately, prolonged use of these drugs is associated with side effects. Topical corticosteroid preparations are widely used for inflammatory dermatological conditions and inhaled corticosteroids account for 55% of the asthma market in the United Kingdom. Prednisolone is the most commonly administered corticosteroid in RA, which though possibly affecting the underlying disease process does not provide a cure and is associated with severe side-effects.

NSAIDs relieve the symptoms of inflammation without altering the course of the disease, but they have adverse gastrointestinal and renal side effects. Their main action is inhibition of arachidonate cyclooxygenase (in inflammatory cells the COX_2 isoenzyme) and thus inhibiting prostaglandin and thromboxane production.

Disease-modifying anti-rheumatic drugs (DMARDs) such as gold products, auranofin (SKB), chloroquine (Sanofi), sulfasalazine (Pharmacia & Upjohn), cyclosporin (Sandoz (Novartis)) and methotrexate (MTX, APH, Pharmacia & Upjohn) are second-line agents for treatment of RA. In most cases their mode of action is ill defined and the term 'slow-acting' is applied because these agents may take weeks or months to have demonstrable effect. Treatment with DMARDs has to be continued for years. If complete remission is achieved for at least six months, the dosage is gradually reduced and may be stopped altogether. DMARDs appear to decrease radiographic joint damage and improve acute-phase markers in RA but they all have adverse effects. In the case of MTX, clinical improvement appears to correlate with inhibition of inflammatory mediators such as interleukins, eicosanoids and tumour necrosis factor (TNF). Combination MTX-cyclosporine therapy has also proven to be

successful in the treatment of patients with severe RA with only partial response to MTX alone.

Diclofenac (o-[(2,6-dichlorophenyl)amino]phenylacetate) is a non-steroidal anti-inflammatory drug of the phenylacetic acid class. When given orally the absorption of diclofenac is rapid and complete. It binds extensively to plasma albumin. Substantial concentrations of drug are attained in synovial fluid, which is the proposed site of action of the NSAIDs. Diclofenac is a potent inhibitor of prostaglandin synthesis and has also been shown to inhibit interleukin-1 (IL-1β) and tumor necrosis factor alpha (TNF-α), involved in osteoarthritis. Gastrointestinal complications such as ulceration and intolerance are the most common adverse effect of diclofenac. Renal dysfunction and hypersensitivity reactions also occur. Many patients with rheumatic disorders have some degree of renal function impairment and are especially susceptible to the induction of renal failure by NSAIDs.

Other non-steroidal anti-inflammatory drugs such as salicylates, indomethacin and ibuprofen directly inhibit cyclooxygenase, a key enzyme in the synthesis pathway of prostaglandins. However, since these drugs inhibit early reactions in the arachidonic acid metabolism, they may block the formation of more than one product, hence leading to severe side effects. Indomethacin, for example, may also disrupt calcium flux across membranes, inhibit cAMP-dependent protein kinase and phosphodiesterase.

It would, therefore, be desirable to be able to extend the usefulness of NSAIDs to conditions that do not respond to lower doses of the drugs and to reduce undesirable side effects by their targeting to the diseased cells.

The use of prodrugs to impart desired characteristics such as increased bioavailability or increased site-specificity for known drugs is a recognized concept in the state of the art of pharmaceutical development. The use of various lipids in the preparation of particular types of prodrugs is also known in the background art. However, none of the background art discloses prodrugs comprising NSAIDs that upon activation by intracellular lipases enable preferential accumulation and release of the drug within the diseased cells.

International Patent Application WO 91/16920 discloses phospholipid prodrugs of salicylates and nonsteroidal anti-inflammatory drugs wherein the drug is directly linked, without any spacer, to either or both of the glycerol hydroxyls of a phospholipid or to available hydroxyls or amines of phospholipid head groups. These prodrugs, when taken orally, protect the gastric mucosa and release the active principle in the gut via the action of pancreatic enzymes.

In other examples of phospholipid prodrugs, the formulation of the prodrugs into liposomes or other micellar structures is the feature that enables their preferential uptake, for instance by liver cells or by macrophages as in the case of the phospholipid conjugates of antiviral drugs disclosed in International Patent Applications WO 93/00910 and WO 90/00555.

International Patent Application WO 96/22780 discloses nonsteroidal anti-inflammatory drugs complexed with zwitterionic, neutral phospholipids. In contrast, the present invention relates to nonsteroidal anti-inflammatory drugs covalently bound to a phospholipid via a spacer group.

U.S Patent No. 5,149,794 discloses a method for delivering drugs selectively to intracellular organelles. The disclosed compounds comprise an antiviral or antineoplastic drug covalently bound to a lipid carrier via a spacer group which may act to modulate drug release at the target site. In contrast to the present invention, the disclosed prodrug is site specific due to the existence of the lipid carrier, and drug release from the lipid conjugate is not a requirement for the drug targeting. In addition, said U.S patent does not disclose phospholipids as the lipid carriers, nor compounds comprising nonsteroidal anti-inflammatory drugs.

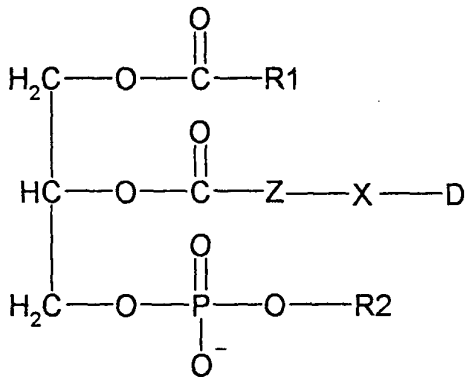
U.S Patent No. 5,256,641 discloses methods of delivering and specifically targeting antigenically-active peptides to cells for the specific production of immunological reactivity against such peptides. In contrast, the present invention does not disclose prodrugs wherein the active ingredients are

peptides, though peptides may serve as a spacer between the active drug and the phospholipid.

U.S Patent No. 5,543,389 discloses covalent polar lipid-drug conjugates for facilitating the entry of drugs into cells at pharmokinetically useful levels. The rationale for specific activation of the prodrug in that case, are very different from the present invention. The examples of the present invention with phospholipids were not made and with hindsight it is clear that it would be ineffective to synthesize active phospholipid prodrugs if the spacer between the lipid and the drug is less than a specific length of at least 4 carbon atoms, because of unfavorable conditions due to steric hindrance and stereochemical problems.

SUMMARY OF THE INVENTION

The present invention provides, in one aspect, compounds of the general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R1 is a saturated or unsaturated, substituted or unsubstituted hydrocarbon chain having from 2 to 30 carbon atoms;
R2 is H or a phospholipid head group;

D is the residue of a nonsteroidal anti-inflammatory drug having a functional group selected from the group consisting of carboxyl, hydroxyl, amine and thiol, wherein D is attached through said functional group to a bridging group, -C(O)-Z-X- , wherein Z is a saturated or unsaturated hydrocarbon chain having from 2 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups, such that when the functional group of D is carboxyl, X is selected from amino, hydroxy and thio, and when the functional group of D is amino, hydroxy or thio, X is a carbonyl group.

In one preferred embodiment, R1 of the above compound of formula I is a hydrocarbon chain having from 10 to 20 carbon atoms, preferably an alkyl residue of 15 or 17 carbon atoms.

According to another preferred embodiment, the nonsteroidal anti-inflammatory drug D is selected from the group including, but not limited to, diclofenac, indomethacin, ibuprofen and naproxen.

In still another preferred embodiment, the phospholipid head group R2 is selected from choline, ethanolamine, inositol and serine.

Preferred according to the invention are compounds of the general formula I wherein the drug residue D is inactive while bound to the -C(O)-Z-X- bridging group and the release of the active drug is initiated by enzymatic cleavage of an ester bond at position sn-2 of the phosholipid. Preferably the enzymatic cleavage is executed by a phospholipase, more preferably phospholipase A_2 (PLA_2).

Most preferred compounds according to the invention are:
1-Stearoyl-2-{3-[2'-(2",6"-dichloroanilino)phenylacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{4-[2'-(2",6"-dichloroanilino)phenylacetamido]butanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{5-[2'-(2",6"-dichloroanilino)phenylacetamido]valeroyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[2'-(2",6"-dichloroanilino)phenylacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{8-[2'-(2",6"-dichloroanilino)phenylacetamido]octanoyl}-sn-glycero-3-phosphatidylcholine'

1-Stearoyl-2-{3-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido] propanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{4-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido] butanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{5-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido] valeroyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido] hexanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{8-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido] octanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{3-[α-methyl-4-(2-methylpropyl)benzeneacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[α-methyl-4-(2-methylpropyl)benzeneacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine,

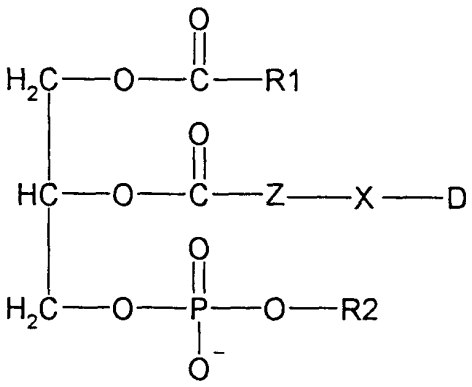
1-Stearoyl-2-{3-[(S)-6-methoxy-α-methyl-2-naphtaleneacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine, and

1-Stearoyl-2-{6-[(S)-6-methoxy-α-methyl-2-naphtaleneacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine.

Compounds of the invention are useful for the treatment of diseases and disorders related to inflammatory conditions. These compounds may serve as prodrugs that upon initial enzymatic cleavage, that may or may not be followed

by further enzymatic or non-enzymatic cleavage(s), release nonsteroidal anti-inflammatory drugs at the diseased site.

Thus, in another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and, as an active ingredient, a compound of the general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R1 is a saturated or unsaturated, substituted or unsubstituted hydrocarbon chain having from 2 to 30 carbon atoms;

R2 is H or a phospholipid head group;

D is the residue of a nonsteroidal anti-inflammatory drug having a functional group selected from the group consisting of carboxyl, hydroxyl, amine and thiol, wherein D is attached through said functional group to a bridging group, -C(O)-Z-X- , wherein Z is a saturated or unsaturated hydrocarbon chain having from 3 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups, such that when the functional group of D is carboxyl, X is selected from amino, hydroxy and thio, and when the functional group of D is amino, hydroxy or thio, X is a carbonyl group,

The pharmaceutical compositions of the invention are useful for the treatment of diseases and disorders related to inflammatory conditions including, but not being limited to, autoimmune diseases such as arthritis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, other diseases such as asthma, psoriasis, inflammatory bowel syndrome, neurological degenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, vascular dementia, and other pathological conditions such as epilepsy, migraines, stroke and trauma.

Any suitable mode of administration of the pharmaceutical composition can be used according to the invention including, but not being limited to, oral, ocular, nasal, parenteral, topical or rectal administration. The pharmaceutical compositions may be in the form of solutions, suspensions, capsules, tablets, aerosols, gels, ointments or suppositories.

In yet another aspect, the invention provides a method for treatment of a disease or disorder related to an inflammatory condition comprising administering to a patient in need thereof a therapeutically effective amount of a compound or a pharmaceutical composition in accordance with the invention.

In still another aspect, the present invention provides a process for the synthesis of compounds in accordance with the invention. Said synthesis process comprising:

(i) providing a molecule y-X-Z-COOH, wherein y is selected from H and OH, Z is a saturated or unsaturated hydrocarbon chain having from 2 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups;

(ii) replacing y with an appropriate blocking group, B;

(iii) preparing an anhydride of the molecule B-X-Z-COOH;

(iv) acylating a lyso-lecithin by the anhydride of step (iii) to yield 1-acyl-2-acyl(X-B)-sn-glycero-3 phospholipid;

(v) removing the blocking group B from the functional group X; and

(vi) coupling a nonsteroidal anti-inflammatory drug D to the functional group X,

thus, generating a molecule of the general Formula I.

Further objects of the present invention will become apparent to those skilled in the art upon further review of the following disclosure, including the detailed descriptions of specific embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a group of novel compounds comprising nonsteroidal anti-inflammatory drugs (NSAIDs) covalently conjugated, via a bridging group, to position sn-2 of a phospholipid.

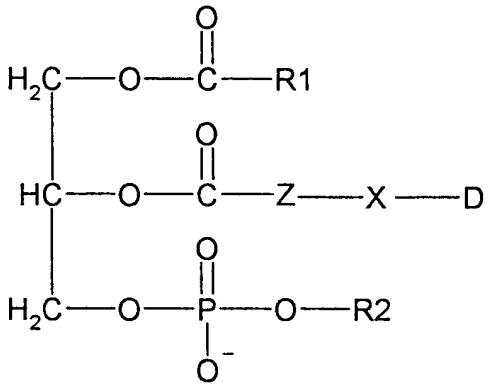
The compounds according to the invention are phospholipid derivatives wherein the conjugated NSAID residue is pharmacologically inactive, and regulated release of the active drug occurs at the site of a diseased tissue. The compounds, being hydrophobic in nature, may penetrate biological membranes and barriers, thus effectively transporting the attached prodrug into cells or organs. The specificity of the activation of the anti-inflammatory prodrug is afforded by the bridging group that is designed to be sensitive to cleavage by phospholipases (e.g. PLA_2) that are specifically elevated at the disease site. Hence, accumulation of the active drug occurs at the site of the disease, whereas, in healthy tissue there will be only a basal level of prodrug cleavage.

It should be appreciated that the novel compounds of the invention wherein the NSAIDs are introduced as prodrugs, are more effective than their corresponding free drugs in at least two aspects: (i) having increased therapeutic efficacy at relatively lower doses, and (ii) exhibiting reduced side effects and toxicity.

Accordingly, it is possible to extend the usefulness of NSAIDs to conditions that do not respond to lower doses of the drug and to reduce undesirable side effects by the regulated release of the active drug at the

diseased site. According to a preferred embodiment, the released drug is identical to the corresponding original drug used for the synthesis of a compound of the invention, hence it is expected to have a similar breadth of therapeutic activity. Also useful are drug derivatives that although released from the phospholipid molecule, remain conjugated to the whole or part of the bridging group, while still capable of exerting therapeutic effects comparable to those of the original drug D.

The compounds of the invention are of the general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R1 is a saturated or unsaturated, substituted or unsubstituted hydrocarbon chain having from 2 to 30 carbon atoms;

R2 is H or a phospholipid head group;

D is the residue of a nonsteroidal anti-inflammatory drug having a functional group selected from the group consisting of carboxyl, hydroxyl, amine and thiol, wherein D is attached through said functional group to a bridging group, -C(O)-Z-X- , wherein Z is a saturated or unsaturated hydrocarbon chain having from 2 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups, such that when the functional group of D is carboxyl, X is selected from amino, hydroxy and thio, and when the functional group of D is

amino, hydroxy or thio, X is a carbonyl group.

It is desired that the generated covalent bond between the bridging group and the drug derivative, i.e. the X-D bond, is a stable ester- , amide- or thioester bond that does not dissociate spontaneously under physiological conditions.

In designing a compound according to the invention, to be used as a prodrug, the specific nature of the inflammatory condition to be treated should be considered. This involves determining the desired pharmacological activity to be achieved hence the choice of the drug D, and identifying the particular site where the desired pharmacological activity is needed.

It should be noted that the number of carbon atoms in said R1 chain of a compound of the general formula I, is determined according to the desired lipophilicity of the molecule. The lipophilicity of the molecule is directly correlated to the selected hydrocarbon chain length. R1 chains according to the invention may contain 2 to 30 carbon atoms. Molecules with R1 having from 10 to 20 carbon atoms are most desired as endowing the molecule with suitable hydrophobicity for crossing biological membranes and at the same time providing adequate substrate for the action of the phospholipase.

R1 may be a saturated or unsaturated hydrocarbon chain, containing one or more double bonds. One or more hydrogen atoms on the chain may be substituted, for example, by halogen atoms or by a small alkyl group such as methyl residues, with the proviso that the substituents still allow free access for the desired cleaving enzymes.

In preferred embodiments of the invention R1 is an alkyl residue of an odd number of carbon atoms. More preferably R1 is an alkyl residue of 15 or 17 carbon atoms yielding, respectively, the naturally occurring palmitoyl (C_{16}) or stearoyl (C_{18}) residues at the α position of the phospholipid.

The selection of the anti-inflammatory drug D comprising the compound of the general formula I is dependent on the disease or disorder intended to be treated. Any nonsteroidal anti-inflammatory drug that possesses a free -C(O)OH, -OH, $-NH_2$, -NH or -SH group available for reaction with the

functional group of the bridging group to form a stable covalent bond D-X, may be selected. Suitable NSAIDs include, but not limited to, drugs presently known on the market, for instance:

1) arylacetic acid derivatives such as diclofenac, etodolac, ibufenac and indomethacin, 2) arylcarboxylic acid derivatives such as ketorolac, 3) aminoarylcarboxylic acid derivatives such as flufenamic acid, meclofenamic acid, mefenamic acid and niflumic acid, 4) arylpropionic acid derivatives such as fenoprofen, ibuprofen, ketoprofen and naproxen, 5) salicylic acid derivatives such as fendosal, mesalamine and salsalate, and 6) thiazinecarboxamides such as piroxicam and tenoxicam.

Also qualified as D are active metabolites or derivatives of NSAIDs that preserve their anti-inflammatory activity provided that they have an available functional group, as mentioned above, readily available for reacting with the appropriate bridging group. A particular example for this kind of drug is the compound 6-methoxy-2-naphthylacetic acid which is an in vivo metabolite of nabumetone [4-(6-methoxy-2-naphthyl)-butan-2-one].

Currently preferred embodiments according to the invention are selected from, but are not limited to, prodrugs wherein D is diclofenac, indomethacin, ibuprofen and naproxen. However, any presently known nonsteroidal anti-inflammatory drugs or those that will be available in the future are included within the scope and concept of the present invention provided that said drugs contain either a carboxyl, hydroxyl, primary or secondary amine or thiol group available for participating in the covalent bond with component X of the bridging group.

It is desirable to provide a compound of the general formula I wherein the anti-inflammatory drug is capable of specifically inhibiting an enzyme which plays a central role in evoking inflammatory processes leading to a disease or disorder, while having no deleterious effects on other basic processes of the cell. Such desirable D drug are, for example, Celecoxib (Searle & Co.) and Meloxicam (Boehringer, Ingelheim) which are capable of differentially inhibiting the enzyme cyclooxygenase 2 (COX 2) induced in inflammatory

cells, and not cyclooxygenase 1 (COX1) which is involved in normal homeostasis.

The choice of the preferred bridging group, -C(O)-Z-X- , is dependent on several considerations; it should participate in a stable covalent bond with the D moiety while lending itself to cleavage at the target site. A preferred bridging group, is such that is resistant to cleavage under normal physiological conditions encountered by the administered compound on its way to the target site. The bridging group should not confer a steric hindrance on the enzymatic cleavage of the ester bond at position sn-2 of the phospholipid of the general formula I.

Depending on the treated inflammatory condition and the particular diseased cell or organs, it will be desirable at times to choose such a bridging group that will regulate the release of the active drug by facilitating or delaying its cleavage from the prodrug molecule.

According to a preferred embodiment, the total number of carbon atoms in the bridging group C(O)-Z-X is at least 6 but at most 15. It was found that this length of carbon chain provides a spacer which enables good access to an enzyme, preferably phospholipase and in particular PLA_2, for digesting the ester bond at position sn-2 of the phospholipid of the general formula I. Shorter spacers, in particular bridging groups comprising less than four carbon atoms, may be problematic, by creating an unfavorable steric environment for the action of the phospholipase. A situation of steric interference may also be generated by long spacers, i.e. when the number of carbon atoms in the bridging chain is greater than 15.

X may be selected from amino, hydroxy, thio and carbonyl groups with the proviso that when the functional group of D is –C(O)OH, X is not a carbonyl, and when the functional group of D is –OH, $–NH_2$, –NH or -SH, X is a carbonyl group.

Some combinations of X with particular drugs may be unfavorable as yielding a very labile bond which is spontaneously cleaved, therefore greatly lowering the efficacy of the prodrug. Such an unfavorable combination is, for

instance, when the functional group of D is a carboxyl group, such as, for example, in diclofenac, forming a covalent bond with X which is a carbonyl group. The resulted bond –(CO)-O-(CO)- is a labile bond that tends to dissociate.

The therapeutic efficacy of any particular compound according to the invention should be evaluated by a person skilled in the art considering the general knowledge in organic chemistry and the teachings of the present invention. The choice of a specific compound to be used as a prodrug according to the invention will also depend on the particular disease or disorder to be treated.

It is suggested that the release of the active drug at the target site is initiated by a first cleavage of the compound at position sn-2 of the phospholipid, preferably by a phospholipase, more preferably phospholipase A_2. PLA_2 is the more preferred cleaving enzyme for two compelling reasons; (i) its enhanced activity is a common feature in many inflammatory processes and (ii) it is abnormally elevated during the progression of the inflammatory disease. Thus, the drug linked to the lipid will preferentially be released at the site of the inflammation due to the increased PLA_2 activity. In accordance with the invention, the phospholipid-NSAID conjugate prodrug is designed to have several distinct advantages over the parent drug, including improved efficacy, potency and pharmacokinetic properties, together with reduced toxicity. It is expected that with the aforementioned advantages, the prodrug compounds of the invention will be efficient alternative novel drugs for inflammatory-related diseases and disorders.

The first cleavage at position sn-2 of the phospholipid, may further facilitate the following cleavage necessary for releasing the active NSAID from the bridging group. This second cleavage may be enzymatically or non-enzymatically executed. Candidate enzymes for performing the second cleavage may include an amidase, esterase or any other suitable enzyme functionally available at the diseased site.

Alternatively, the release of an active anti-inflammatory drug from the D-X bond may be initiated by any cleavage at position sn-2 of the phospholipid that leads to release of an active drug. Moreover, under some circumstances the active drug released may be different from the original parent drug molecule. This includes drug derivatives wherein a chemical group(s) has been removed from or added to the D structure. These cases are also included within the concept of the invention provided that the resulted drug derivative preserves its therapeutic capability. Preferably the cleavage process of the molecule of the invention is initiated specifically at the diseased cells, thus generating a highly specific and highly effective drug released at the desired target site.

Irrespective of the exact mechanism of action, it is evident that the novel compounds of the invention have an enhanced therapeutic profile. Furthermore, they are more effective than their corresponding parent drugs in at least two aspects: (i) increased specificity, and (ii) decreased side effects. The compounds of the invention may enable extending the usefulness of NSAIDs to conditions that do not respond to lower doses of the drug as well as reducing undesirable side effects by preferential releasing of the active drug at the diseased site.

In accordance with another aspect of the invention, there are provided pharmaceutical compositions comprising as an active ingredient a compound of the general formula I wherein Z of the bridging group having 3 to 15 carbon atoms, and a pharmaceutically acceptable diluent or carrier as are known in the art.

The pharmaceutical compositions may be in a liquid, aerosol or solid dosage form, and may be formulated into any suitable formulation including, but not limited to, solutions, suspensions, micelles, emulsions, microemulsions, aerosols, ointments, gels, suppositories, capsules, tablets, and the like, as will be required for the appropriate route of administration.

Compounds of the invention are useful in the treatment of diseases and disorders related to an inflammatory condition. Thus, in yet another aspect, the present invention provides a method for treating such an inflammatory-related disease or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of the general formula I or a

pharmaceutical composition in accordance with the invention. The term "therapeutically effective amount" used in the specification refers to the amount of a given prodrug compound according to the invention which antagonizes or inhibits activities associated with inflammatory processes, hence providing either a subjective relief of a symptom(s) or an objectively identifiable improvement as noted by the clinician or other qualified observer.

In particular, the present invention provides a method for treating a disease or disorder related to inflammatory condition including, but not being limited to, autoimmune diseases such as arthritis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, other diseases such as asthma, psoriasis, inflammatory bowel syndrome, neurological degenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, vascular dementia, and other pathological conditions such as epilepsy, migraines, stroke and trauma.

Any suitable route of administration is encompassed by the invention including, but not being limited to, oral, intravenous, intramuscular, subcutaneous, inhalation, intranasal, topical, rectal or other known routes. In preferred embodiments, the pharmaceutical compositions of the invention are orally or nasally administered.

The dose ranges for the administration of the compositions of the invention are those large enough to produce the desired protective effect. The dosing range of the prodrug varies with the specific drug used, the treated inflammatory condition or neurological disorder, the route of administration and the potency of the particular prodrug molecule in releasing the drug at the specific target site. The dosage administered will be dependent upon the age, sex, health, weight of the recipient, concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Dosage regimen and means of administration will be determined by the attending physician or other person skilled in the art.

In still another aspect, the present invention provides a method for synthesizing compounds of the above-defined formula I by following the steps

of the detailed scheme of synthesis described hereinbelow. A particular synthesis scheme is depicted in Scheme I and exemplified in Examples 1 to 4. Generally speaking the synthesis process involves the following steps:

Step 1: protection of the functional moiety X on the bridging group. The purpose of this step is to prevent chemical reactions of X during the coupling of the bridging group to the lyso-lecithin molecule, so that linking of the bridging group to the lipid is exclusively mediated through the carboxyl group of the linker HO(O)C-Z-X.

Any blocking group that reacts with the functional moiety X to mask its reactive function and is readily removable after coupling, may be employed. Reagents suitable for use as protecting groups are well known to those skilled in the art and include, but are not limited to, the following: benzyl chloromate, benzyloxycarbonate (for NH_2 or NH protection), benzyloxymethyl chloride, dihydropyran (for OH protection), diphenylcarbinol, trimethylacetamidocarbinol (for SH protection) and methoxymethyl chloride (for COOH protection).

Appropriate blocking reagents and protocols for their usage are described in *Protecting Groups* by Kocienski, P. (Thieme foundation of organic chemistry series, 1994) and in *Protective Groups in Organic Synthesis* by Greene, T. and Wuts, P. (John Wiley & Sons, Inc. 1991), the teachings of which are incorporated herein by reference.

Step 2: Preparation of an anhydride of the protected bridging group. The formation of the anhydride is performed by employing a reagent which removes one molecule of water from two protected bridging groups. This reaction is preferably performed under inert atmosphere. A commonly used reagent for this reaction is, for example, dicyclohexylcarbodiimide (DCC).

Step 3: Coupling of the protected bridging group to a lyso-lecithin. This step is carried out by acylating the appropriate phospholipid at position sn-2 to yield 1-acyl-2-acyl(X-protected)-sn-glycero-3 phospholipid. The anhydride of the protected bridging group and the corresponding lyso-lecithin are dissolved in organic solvent, for example chloroform or methylene

chloride, in the presence of a catalyst, for example a tret-amine such as dimethylaminopyridine (DMAP).

Step 4: Removal of the blocking group from the functional group X. Protocols for removal of the blocking groups used in step 1 for protecting the functional group X, are disclosed in *Protecting Groups* by Kocienski, P. (Thieme foundation of organic chemistry series, 1994) and in *Protective Groups in Organic Synthesis* by Greene, T. and Wuts, P. (John Wiley & Sons, Inc. 1991). In a particular procedure, the protecting group is removed by hydrogenation in the presence of Pd/C.

Step 5: Coupling a nonsteroidal anti-inflammatory drug to the lipid moiety.

Coupling of the corresponding drug to the functional group X of the bridging group is the last stage in the protocol for the synthesis of the compounds in accordance with the invention. This reaction is conducted in an organic solvent in the presence of reagents that enable a condensation reaction where water molecules are removed. Such commonly used reagents are, for example, the combination of triphenylphosphine and aldrithiol-2.

Contrary to other known procedures for the synthesis of lipid derivatives of drugs, the present protocol is unique in designating the drug conjugation step as the final one. It is important that the drug is added at the last step in order to prevent possible modifications and deterioration to its structure. Thus the process disclosed in the present invention is advantageous in terms of higher yield of the desired reaction product and much reduced levels of side products.

In a preferred embodiment, the reacting functional groups that form the X-D bond are -C(O)OH and NH_2 or NH groups, yielding a peptide bond. The carboxyl or the amino groups may be provided by either group X on the bridging group, or as an available functional group on the drug molecule. According to that preferred embodiment, when the reacting group of the drug is a carboxyl, it is reacted with an amine on the bridging group, and vice versa, when the reacting group of the drug is an amine, its reacting counterpart on the bridging group is a carboxyl.

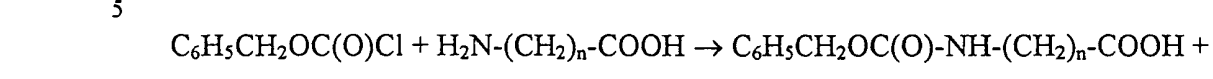
EXAMPLES:

A particular scheme for the synthesis of compounds of the invention is outlined in Scheme I. This scheme is exemplified below, in Examples 1 to 4, by the detailed description of the synthesis of specific lipid derivatives of diclofenac (o-(2,6-dichloroanilino)phenyl acetic acid), indomethacin, (1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid), ibuprofen (2-(4-isobutylphenyl)propionic acid) and naproxen (d-2-(6-methoxy-2-naphthyl)propionic acid) conjugated to phosphatidylcholine. This synthesis is a six-stage process: The first stage is protection of the functional group on the linker, in this case the amino group of an amino acid. The second stage is preparation of anhydride of this protected amino acid. The third stage is the formation of lipid derivative comprising the protected amino acid and a lyso-lecithin. The removal of the protecting group to yield the amino acid lipid conjugate is carried out in the fourth and fifth stages. Linking of the corresponding drug, in these particular examples, diclofenac, indomethacin, ibuprofen or naproxen, to 1-acyl-2-(n-amino)acyl-sn-glycero-3-phosphatidylcholine is realized in the last stage.

Scheme I

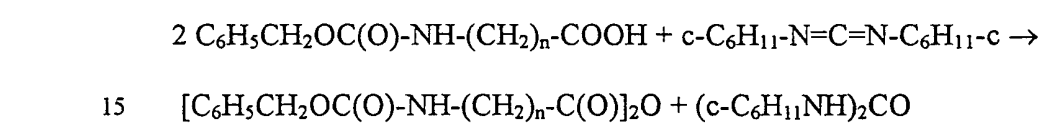
A scheme for synthesis of phosphatidylcholine derivatives of diclofenac, indomethacin, ibuprofen and naproxen.

Step 1:



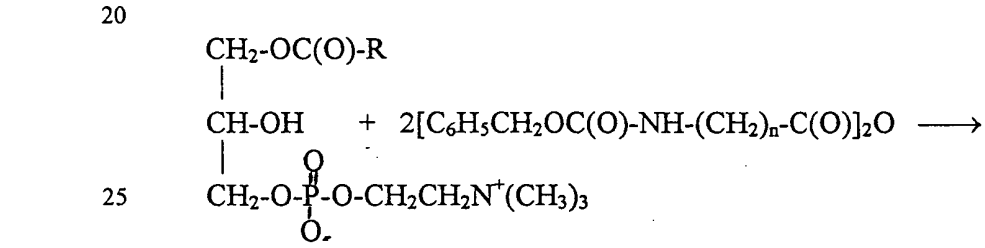
$$C_6H_5CH_2OC(O)Cl + H_2N\text{-}(CH_2)_n\text{-}COOH \rightarrow C_6H_5CH_2OC(O)\text{-}NH\text{-}(CH_2)_n\text{-}COOH + HCl.$$

Step 2:

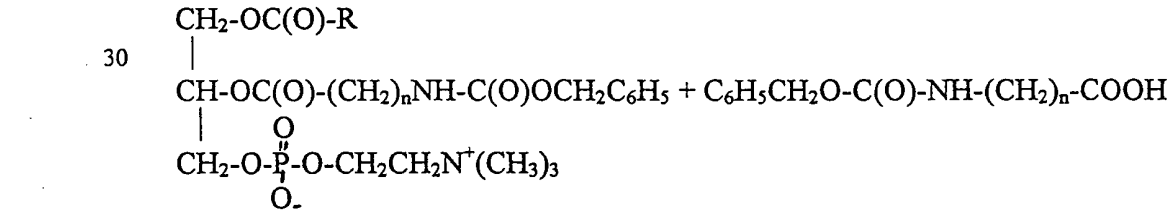


$$2\ C_6H_5CH_2OC(O)\text{-}NH\text{-}(CH_2)_n\text{-}COOH + c\text{-}C_6H_{11}\text{-}N{=}C{=}N\text{-}C_6H_{11}\text{-}c \rightarrow [C_6H_5CH_2OC(O)\text{-}NH\text{-}(CH_2)_n\text{-}C(O)]_2O + (c\text{-}C_6H_{11}NH)_2CO$$

Step 3:

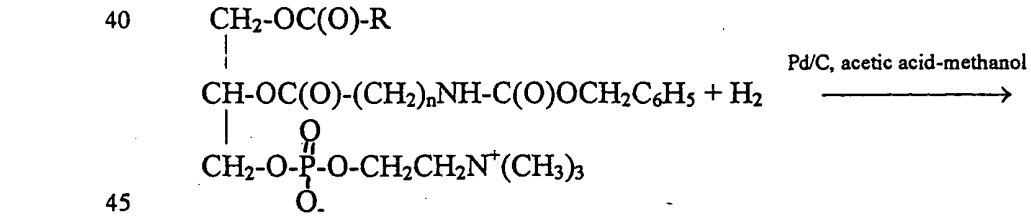


$$\begin{array}{l} CH_2\text{-}OC(O)\text{-}R \\ | \\ CH\text{-}OH \\ | \\ CH_2\text{-}O\text{-}P(=O)(O^-)\text{-}O\text{-}CH_2CH_2N^+(CH_3)_3 \end{array} + 2[C_6H_5CH_2OC(O)\text{-}NH\text{-}(CH_2)_n\text{-}C(O)]_2O \longrightarrow$$

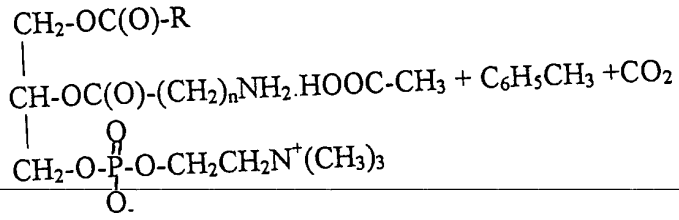


$$\begin{array}{l} CH_2\text{-}OC(O)\text{-}R \\ | \\ CH\text{-}OC(O)\text{-}(CH_2)_nNH\text{-}C(O)OCH_2C_6H_5 \\ | \\ CH_2\text{-}O\text{-}P(=O)(O^-)\text{-}O\text{-}CH_2CH_2N^+(CH_3)_3 \end{array} + C_6H_5CH_2O\text{-}C(O)\text{-}NH\text{-}(CH_2)_n\text{-}COOH$$

Step 4:



$$\begin{array}{l} CH_2\text{-}OC(O)\text{-}R \\ | \\ CH\text{-}OC(O)\text{-}(CH_2)_nNH\text{-}C(O)OCH_2C_6H_5 \\ | \\ CH_2\text{-}O\text{-}P(=O)(O^-)\text{-}O\text{-}CH_2CH_2N^+(CH_3)_3 \end{array} + H_2 \xrightarrow{\text{Pd/C, acetic acid-methanol}}$$



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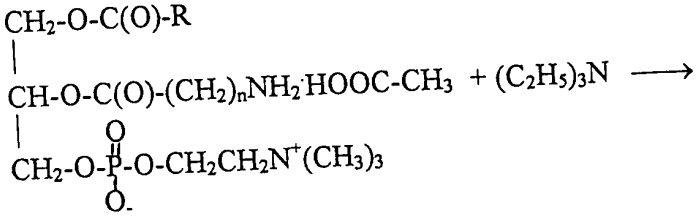
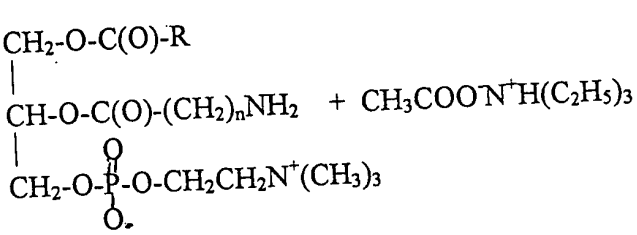
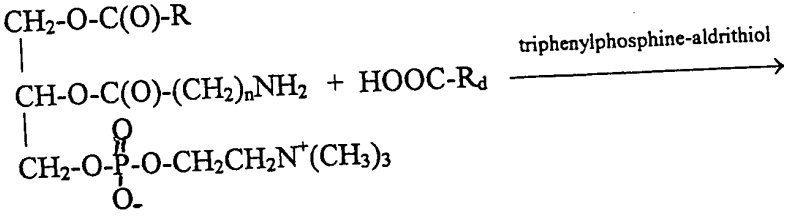
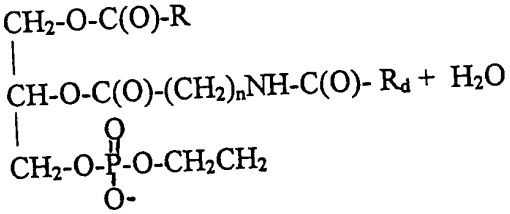


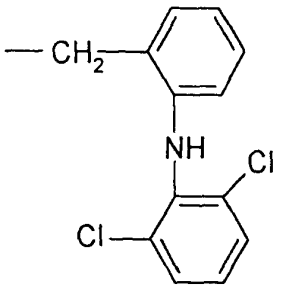


Step 6:

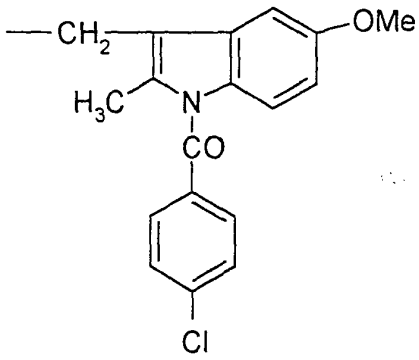


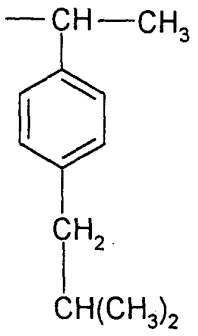


Diclofenac

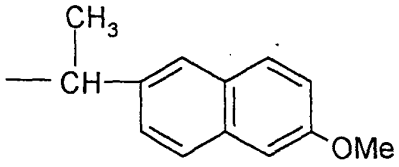


Indomethacin





Ibuprofen



Naproxen

R_d = Nonsteroidal anti-inflammatory drug residue

EXAMPLE 1: Preparation of lipid derivatives of diclofenac (DP-DFC)

Stage 1. Protection of the amino group of amino acid (Preparation of Z-amino acid).

To a mixture of 0.1 mol corresponding amino acid (aminopropanoic acid, aminobutanoic acid, aminovaleric acid, aminohexanoic acid or aminooctanoic acid) in ethanol (25 ml) in round-bottom flask (250 ml) equipped with a magnetic stirrer and dropped funnel, a solution of NaOH (8.8g.,

0.22 mol) in 100 ml water is added and the mixture is stirred by magnetic stirrer until fully dissolved. The obtained solution is cooled to 0^0C in an ice-water bath, and benzyl chloroformate (27.4g , 0.15 mol) is added drop wise over 30 min. The reaction mixture is stirred for 3 hours at 0^0C. Subsequently, about 100 ml water is added to the reaction solution and the mixture is poured into separated funnel. The solution is washed with diethyl ether (3X 50 ml). The water fraction is separated and acidified with HCl (3N) to pH=1 while cooling in an ice-water bath. If a precipitate is formed, it is filtered, washed with water and dissolved in 100 ml chloroform. The chloroform solution is dried with sodium sulfate for two hours. Then the sodium sulfate is separated from the chloroform solution by filtration and the solvent is evaporated in evaporator under vacuum. The residue is washed with hexane, and dried overnight in vacuum over phosphorus pentoxide (P_2O_5).

If the precipitate is not formed, or in order to maximize the product yield, the acidified aqueous fraction is washed with chloroform (2X 50 ml). The chloroform extracts are combined and washed with water (50ml). The following operations with this solution are the same as for the above-described chloroform solution of the precipitate, namely, drying with sodium sulfate for two hours, then separating the sodium sulfate from the chloroform solution by filtration and evaporating the solvent in evaporator under vacuum. The residue is then washed with hexane, and dried overnight in vacuum over phosphorus pentoxide (P_2O_5).

All products were analyzed on TLC as follows:

TLC analysis. Silica gel 60 on aluminum sheet. Eluent is chloroform-methanol (4:1 v/v). Indicator is a spray of the composition: 4-methoxybenzaldehyde (10ml), absolute ethanol (200ml), 98% sulfuric acid (10ml) and glacial acetic acid (2ml). The chromatogram is sprayed with the indicator and then charred using hot air at 150-180^{0}C.

The following are the intermediate products resulted at the end of stage 1 of the synthesis procedure:

3-(Carbobenzyloxyamino)propanoic acid. C_6H_5-CH_2-O-C(O)-NH-CH_2-CH_2-COOH.

White solid. Yield 60%. TLC analysis: One spot R_f 0.7.

^{1}H NMR (CD_3OD), δ(ppm): 2.46-2.52 (t, 2H.), 3.29-3.39 (t, 2H.) 5.06 (s, 2H), 7.27-7.32 (m, 5H).

4-(Carbobenzyloxyamino)butanoic acid. $C_6H_5CH_2$-O-C(O)-NH-$(CH_2)_3$-COOH.

White solid. Yield 60%. TLC analysis: One spot. R_f 0.7.

^{1}H NMR (CD_3OD), δ (ppm): 1.71-1.82 (m, 2H), 2.28-2.34 (t, 2H), 3.10-3.17 (t, 2H), 5.06 (s, 2H), 7.26-7.34 (m, 5H).

5-(Carbobenzyloxyamino)valeric acid. $C_6H_5CH_2$-O-C(O)-NH-$(CH_2)_4$-COOH.

White solid. Yield 60%. TLC analysis: One spot. R_f 0.7.

^{1}H NMR (CD_3OD), δ (ppm): 1.45-1.50 (m, 2H), 1.56-1.62 (m, 2H), 2.25-2.31 (t, 2H), 3.08-3.13 (t, 2H), 5.05 (s, 2H), 7.26-7.34 (m, 5H).

6-(Carbobenzyloxyamino)hexanoic acid. $C_6H_5CH_2$-O-C(O)-NH-$(CH_2)_5$-COOH.

White solid. Yield 50%. m.p. 54-56^{0}C. TLC analysis: One spot. R_f 0.7.

^{1}H NMR (CD_3OD), δ (ppm): 1.30-1.63 (several m, 6H), 2.24-2.30 (t, 2H), 3.07-3.13 (t, 2H), 5.05 (s, 2H), 7.29-7.34 (m, 5H).

8-(Carbobenzyloxyamino)octanoic acid. $C_6H_5CH_2$-O-C(O)-NH-$(CH_2)_7$-COOH.

White solid. Yield 50%. TLC analysis: One spot. R_f 0.7.

^{1}H NMR (CD_3OD), δ (ppm): 1.32 (broad s, 6H), 1.47-1.50 (m, 2H), 1.53-1.59 (m, 2H), 2.23-2.29 (t, 2H), 3.06-3.12 (t, 2H), 5.05 (s, 2H), 7.29-7.34 (s, 5H).

Stage 2. Synthesis of Z-amino acid anhydride.

The solution of corresponding Z-aminoacid produced at stage 1 (0.05 mol) in freshly distilled dichloromethane (25 ml) is introduced, under an inert atmosphere of argon, into double-neck round-bottom equipped with magnetic

stirrer and dropped [redacted]nel. A solution of dicyclohexylcarbodiimide (0.0325 mol) in 25 ml of freshly distilled dichloromethane, also under argon, is added drop wise, with stirring, to the solution of Z-amino acid. After 20 min of stirring, the obtained precipitate of urea is filtered and the solution evaporated under vacuum. The crude residue is washed with hexane (2X 20 ml) and then dried in vacuum.

TLC analysis: The same procedure is used for TLC analysis of the anhydrides of all Z-amino-acids. Silica gel 60 on aluminum sheet. Fluent is the mixture of chloroform with acetone (8:2, v/v). For indication, ninhydrine spray is used on the chromatogram followed by charring with hot air (100 ^{0}C).

Anhydride of Z-(3-amino)propanoic acid.

White solid. Yield is 70%. TLC analysis: One spot R_f 0.8.

Chemical analysis. $C_{22}H_{24}N_2O_7$. Calculated: C 61.68%, H 5.60%, N 6.54%. Found: C 61.20%, H 5.52%, N 6.50%.

Anhydride of Z-(4-amino)butanoic acid.

White solid. Yield is 70%. TLC analysis: One spot. R_f 0.8.

Chemical analysis. $C_{24}H_{28}N_2O_7$. Calculated: C 63.16%, H 6.14%, N 6.14%. Found: C 62.77%, H 6.36%, N 5.88%.

Anhydride of Z-(5-amino)valeric acid.

White solid. Yield is 70%. TLC analysis: One spot. R_f 0.8.

Chemical analysis. $C_{26}H_{32}N_2O_7$. Calculated: C 64.46%, H 6.61%, N 5.78%. Found: C 64.09%, H 6.86%, N 5.49%.

Anhydride of Z-(6-amino)hexanoic acid.

White solid. Yield is 70%. TLC analysis: One spot. R_f 0.8.

Chemical analysis: $C_{28}H_{36}N_2O_7$. Calculated: C 64.46%, H 6.61%, N 5.79%. Found: C 64.39%, H 6.85%, N 5.52%.

Anhydride of Z-(8-amino)octanoic acid.

White solid. Yield is 75%. TLC analysis: One spot. R_f 0.85.

Chemical analysis: $C_{32}H_{44}N_2O_7$. Calculated: C 67.60%, H 7.75%, 4.93%.

Found: C 67.44%, 7.79%, N 4.72%.

Stage 3. Preparation of 1-acyl-2- (Z-amino)acyl-sn-glycero-3-phosphotidylcholine.

The anhydride of the corresponding Z-amino acid, 0.01 mol dissolved in 150 ml of freshly distilled chloroform, is introduced, under an inert atmosphere of argon, into a single-neck round-bottom flask (250 ml) equipped with a magnetic stirrer. To this solution 0.01 mol (1.22 g) 4-(dimethylamino)pyridine (DMAP) in 25 ml chloroform is added, followed by addition of a suspension of 0.0056 moles lyso-lecithin in 50 ml of chloroform. The reaction mixture is vigorously stirred for 3-5 hours at room temperature. The lyso-lecithin dissolves and reaction mixture becomes transparent after about 2 hours of stirring. The reaction is monitored by TLC using silica gel 60 on aluminum sheet, the eluent is chloroform:methanol:water, 65:35:5, the indicator is a spray of the composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator followed by charring with hot air at 150^0C. The reaction is assumed to be complete and stopped when all the lyso-lecithin has disappeared. The reaction mixture is then transferred into a separating funnel and washed with a solution of 1% HCl (3x 50 ml), then with saturated solution of sodium bicarbonate (3x 50 ml) and finally with water (3x 50 ml). The obtained product in the organic solution is dried over sodium sulfate and then filtered. The solvent is evaporated at 30^0C in vacuo and the residue is washed with hexane and left to dry overnight under vacuum. The resulted molecule 1-acyl-2-(Z-amino)acyl-sn-glycero-3-phosphatidylcholine is the main product of the reaction.

The second product of the reaction is the Z-amino acid. In order to increase the yield of this product, it is back-extracted from reaction mixture as

follows: The sodium bicarbonate aqueous fractions are collected and combined and then acidified by 3 N HCl to pH 1. The Z-amino acid is extracted by chloroform (2x 50 ml). The chloroform extracts were combined, washed once with water and dried over sodium sulfate for 30 min with stirring. The sodium sulfate is removed by filtration, and the chloroform evaporated. Subsequently, the residue is washed with hexane and dried over P_2O_5 in vacuo.

TLC analysis: Silica gel 60 on aluminum sheet. Eluent is chloroform/methanol/water (65:35:5, v/v). Indicator is a spray of the composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred using hot air at 100-150^{0}C.

1-Stearoyl-2-[3'-(carbobenzyloxyamino)]propanoyl-sn-glycero-3-phosphotidyl choline.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.55

^{1}H NMR ($CDCl_3$), δ (ppm): 0.83-0.89 (t, 3H), 1.23-1.27 (broad s, 28H), 1.54 (m, 2H), 2.22-2.29 (t, 2H), 2.53-2.56 (m, 2H), 3.15 (s, 9H), 3.41-3.44 (m, 2H), 3.60-3.63 (m, 2H), 3.85-3.96 (m, 2H), 4.13-4.25 (m, 4H), 5.05 (s, 2H), 5.20 (m, 1H), 7.27-7.33 (m, 5H).

1-Stearoyl-2-[4'-(carbobenzyloxyamino)]butanoyl-sn-glycero-3-phosphotidyl choline.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.55.

^{1}H NMR ($CDCl_3$), δ (ppm): 0.84-0.88 (t, 3H), 1.25 (broad s, 28H), 1.52-1.55 (m, 2H), 1.72-1.80 (m, 2H), 2.23-2.32 (m, 4H), 3.07-3.14 (m, 2H), 3.18 (s, 9H), 3.61-3.65 (m, 2H), 3.86-3.94 (m, 2H), 4.10-4.25 (m, 4H), 5.06 (s, 2H), 5.22 (m, 1H), 7.26-7.33 (m, 5H).

1-Stearoyl-2-[5'-(carbobenzyloxyamino)]valeroyl-sn-glycero-3-phosphotidyl choline.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.55.

^{1}H NMR ($CDCl_3$), δ (ppm): 0.84-0.89 (t, 3H), 1.26 (broad s, 28H), 1.54-1.65 (m, 4H), 1.72-1.77 (m, 2H), 2.23-2.30 (m, 4H), 3.07-3.12 (m, 2H), 3.16 (s, 9H), 3.61-3.65 (m, 2H), 3.86-3.94 (m, 2H), 4.10-4.25 (m, 4H), 5.06 (s, 2H), 5.20 (m, 1H), 7.26-7.33 (m, 5H).

1-Stearoyl-2-[6'-(carbobenzyloxyamino)]hexanoyl-sn-glycero-3-phosphotidyl choline.

White wax. Yield 65%. TLC analysis: One spot. R_f 0.55.

^{1}H NMR ($CDCl_3$), δ (ppm): 0.84-0.89 (t, 3H), 1.24 (broad s, 28H), 1.30-1.62 (several m, 8H), 2.22-2.30 (m, 4H), 3.06-3.12 (m, 2H), 3.15 (s, 9H), 3.61-3.65 (m, 2H), 3.88-3.97 (m, 2H), 4.10-4.25 (m, 4H), 5.05 (s, 2H), 5.20 (m, 1H), 7.25-7.32 (m, 5H).

1-Stearoyl-2-[8'-(carbobenzyloxyamino)]octanoyl-sn-glycero-3-phosphotidyl choline.

White wax. Yield 65%. TLC analysis: One spot. R_f 0.55.

^{1}H NMR ($CDCl_3$), δ (ppm): 0.84-0.89 (t, 3H), 1.25 (broad s, 28H), 1.30-1.33 (m, 6H), 1.46-1.49 (m, 2H), 1.52-1.58 (m, 4H), 2.22-2.29 (m, 4H), 3.05-3.10 (m, 2H), 3.17 (s, 9H), 3.61-3.65 (m, 2H), 3.85-3.96 (m, 2H), 4.10-4.23 (m, 4H), 5.06 (s, 2H), 5.20 (m, 1H), 7.22-7.29 (m, 5H).

Stage 4. Removal of the protecting benzyloxycarbonyl group.

The obtained 1-stearoyl-2-(carbobenzyloxyamino)acyl-3-phosphotidyl-choline (0.0025 mol) is dissolved in a mixture of 100 ml methanol and 5 ml acetic acid. The solution is introduced into round bottom double neck flask (200 ml) equipped with a magnetic stirrer, under an atmosphere of argon. Pd/C (0.5 g) is added to the solution and hydrogen is blown through the reaction mixture for 4 hours. The reaction proceeding is monitored by TLC analysis under the following conditions: silica gel 60 on aluminum sheet, eluent is the mixture of chloroform/methanol/water (65:35:5, v/v), indicator is a spray of the composition: p-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98%

sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred using hot air at 100-150^{0}C.

The reaction assumed to be complete and hydrogenation is stopped after all corresponding 1-stearoyl-2-carbobenzyloxyaminoacyl-sn-glycero-phosphatidylcholine has disappeared. The reaction mixture is then filtered through celete to remove the Pd/C, evaporated at 30^{0}C, under vacuum. The crude residue is washed with ether (3x 30 ml) and dried in vacuo overnight. Conditions of the TLC analysis are the same as indicated above.

1-Stearoyl-2-(3-amino)propanoyl-sn-glycero-3-phosphatidylcholine, acetic acid.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.2.

^{1}H NMR (CD_3OD), δ (ppm): 0.87-0.92 (t, 3H), 1.28 (broad s, 28H), 1.58-1.61 (m, 2H), 1.92 (s, 3H), 2.30-2.38 (t, 2H), 2.71-2.77 (t, 2H), 3.17-3.19 (m, 2H), 3.22 (s, 9H), 3.62-3.65 (m, 2H), 3.87-4.48 (several m, 6H), 5.24 (m, 1H).

^{31}P NMR (CD_3OD), δ (ppm): 0.01 (s).

Chemical analysis: $C_{29}H_{59}N_2O_8P.CH_3COOH$. Calculated: C 56.88%, H 9.63%, N 4.28%, P 4.74%. Found: C 57.01%, H 10.11%, N 4.18%, P 4.52%.

1-Stearoyl-2-(4-amino)butanoyl-sn-glycero-3-phosphatidylcholine, acetic acid.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.2.

^{1}H NMR (CD_3OD), δ (ppm): 0.86-0.92 (t, 3H), 1.28 (broad s, 28H), 1.56-1.60 (m, 2H), 1.94 (s, 3H), 1.96-1.99 (m, 2H), 2.29-2.35 (t, 2H), 2.46-2.52 (m, 2H), 2.95-3.02 (t, 2H), 3.22 (s, 9H), 3.62-3.66 (m, 2H), 3.87-4.46 (several m, 6H), 5.21-5.22 (m, 1H).

^{31}P NMR (CD_3OD), δ (ppm): 0.01 (s).

Chemical analysis: $C_{30}H_{61}N_2O_8P.CH_3COOH$. Calculated: C 57.48%, H 9.73%, N 4.19%, P 4.64%. Found: C 57.12%, H 9.55%, N 4.22%, P 4.38%.

1-Stearoyl-2-(5-amino)valeroyl-sn-glycero-3-phosphatidylcholine, acetic acid.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.2.

^{1}H NMR (CD_3OD), δ (ppm): 0.87-0.92 (t, 3H), 1.27 (broad s, 28H), 1.55-1.61 (m, 2H), 1.92 (s, 3H), 1.96-2.10 (m, 2H), 2.29-2.35 (t, 2H), 2.46-2.52 (m, 2H), 2.95-3.02 (t, 2H), 3.22 (s, 9H), 3.62-3.66 (m, 2H), 3.85-4.46 (several m, 6H), 5.19-5.21 (m, 1H).

^{31}P NMR (CD_3OD), δ (ppm): 0.01 (s).

Chemical analysis: $C_{31}H_{63}N_2O_8P.CH_3COOH$. Calculated: C 58.06%, H 9.82%, N 4.05%, P 4.54%. Found: C 57.90%, H 10.01%, N 4.20%, P 4.48%.

1-Stearoyl-2-(6-amino)hexanoyl-sn-glycero-3-phosphatidylcholine, acetic acid.

White wax. Yield 65%. TLC analysis: One spot. R_f 0.2.

^{1}H NMR (CD_3OD), δ (ppm): 0.86-0.92 (t, 3H), 1.28 (broad s, 28H), 1.32-1.50 (m, 2H), 1.56-1.72 (broad m, 6H), 1.91 (s, 3H), 2.28-2.40 (broad m, 4H), 2.88-2.94 (t, 2H), 3.22 (s, 9H), 3.61-3.66 (m, 2H), 3.95-4.08 (m, 2H), 4.10-4.38 (several m, 4H), 5.24 (m, 1H).

^{31}P NMR (CD_3OD), δ (ppm): 0.01 (s).

Chemical analysis: $C_{32}H_{65}N_2O_8P.CH_3COOH$. Calculated: C 58.62%, H 9.91%, N 4.02%, P 4.45%. Found: C 58.19%, H 10.11%, N 4.12%, P 4.58%.

1-Stearoyl-2-(8-amino)octanoyl-sn-glycero-3-phosphatidylcholine, acetic acid.

White wax. Yield 65%. TLC analysis: One spot. R_f 0.2.

^{1}H NMR (CD_3OD), δ (ppm): 0.86-0.92 (t, 3H), 1.28 (broad s, 28H), 1.37 (s, 6H), 1.59-1.67 (broad m, 6H), 1.93 (s, 3H), 2.28-2.39 (broad m, 4H), 2.86-2.92 (t, 2H), 3.22 (s, 9H), 3.62-3.66 (m, 2H), 3.97-4.03 (m, 2H), 4.13-4.39 (several m, 4H), 5.22-5.23 (m, 1H).

^{31}P NMR (CD_3OD), δ (ppm): 0.01 (s).

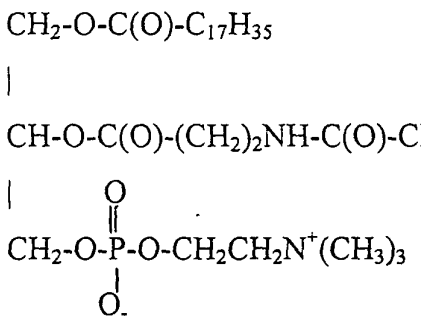
Chemical analysis: $C_{34}H_{69}N_2O_8P.CH_3COOH$. Calculated: C 59.67%, H 10.08%, N 3.87%, P 4.28%. Found: C 59.22%, H 10.21%, N 3.99%, P 4.08%.

Lipid derivatives of diclofenac (DP-DFC)

All the synthesized products mentioned below are pale yellow solids that when analyzed by TLC are displayed in one bright red spot, R_f is 0.3.

The TLC analysis conditions are as follows: Silica gel 60 on aluminum sheet. Eluent is chloroform:methanol:water (65:35:5, v/v). Indicator is a spray of the composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred at 100^0C.

1-Stearoyl-2-{3-[2'-(2",6"-dichloroanilino)phenylacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine.



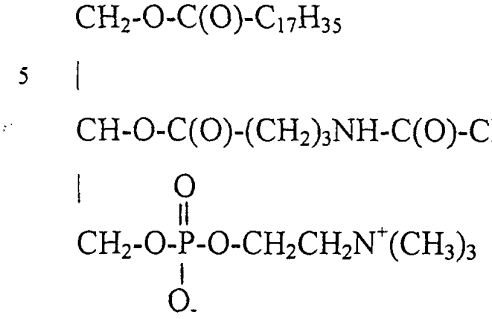
Yield 75%.

^{1}H NMR (CD_3OD), δ (ppm): 0.84-0.89 (t, 3H), 1.26 (broad s, 28H), 1.54-1.59 (m, 2H), 2.27-2.33 (t, 2H), 2.56-2.61 (t, 2H), 3.18 (s, 9H), 3.44-3.49 (t, 2H), 3.58-3.61 (m, 2H), 3.68 (s, 2H), 4.02-4.05 (m, 2H), 4.19-4.26 (m,3H), 4.36-4.38 (m, 1H), 5.21-5.25 (m, 1H), 6.36-6.40 (d, 1H), 6.84-6.90 (t, 1H), 7.02-7.09 (m,2H), 7.20-7.24 (d, 1H), 7.37-7.41 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.84 (s).

Chemical analysis: $C_{43}H_{68}N_3O_9PCl_2.2H_2O$. Calculated: C 56.83%, H 7.93%, N 4.62%, P 3.41%. Found: C 57.01%, H 7.59%, N 4.27%, P 3.39%.

1-Stearoyl-2-{4-[2'-(2",6"-dichloroanilino)phenylacetamido]butanoyl}-sn-glycero-3-phosphatidylcholine.



Yield 75%.

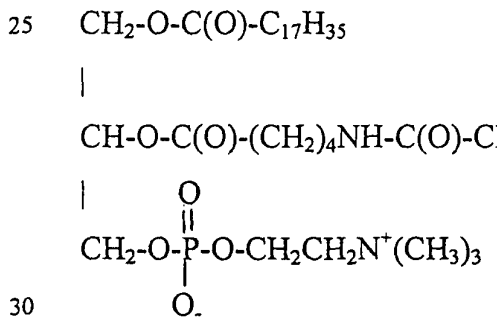
^{1}H NMR (CD_3OD), δ (ppm): 0.86-0.90 (t, 3H), 1.25 (broad s, 28H), 1.53-1.57 (m, 2H), 1.80-1.84 (m, 2H), 2.27-2.31 (t, 2H), 2.36-2.41 (t, 2H), 3.17 (s, 9H), 3.19-3.25 (m, 2H), 3.57-3.60 (m, 2H), 3.66 (s, 2H), 4.00-4.03 (m, 2H), 4.17-4.25 (m, 3H), 4.37-4.41 (m, 1H), 5.21-5.25 (m, 1H), 6.37-6.40 (d, 1H), 6.85-6.89 (t, 1H), 7.01-7.07 (m, 2H), 7.19-7.22 (d, 1H), 7.37-7.40 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.88 (s).

MS: $C_{44}H_{70}N_3O_9PCl_2$, Found m/e:886.9 (FAB) (main pick).

Chemical analysis: $C_{44}H_{70}N_3O_9PCl_2.2H_2O$. Calculated: C 57.27%, H 8.03%, N 4.56%, P 3.36%. Found: C 57.21%, H 8.11%, N 4.61%, P 3.32%.

1-Stearoyl-2-{5-[2'-(2",6"-dichloroanilino)phenylacetamido]valeroyl}-sn-glycero-3-phosphatidylcholine.



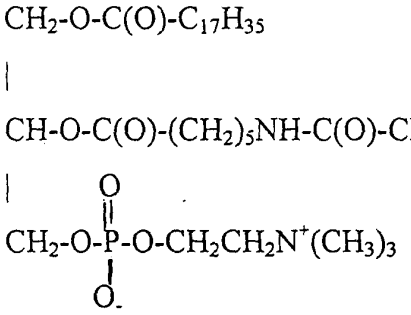
Yield 75%.

^{1}H NMR (CD_3OD), δ (ppm): 0.83-0.89 (t, 3H), 1.24 (broad s, 28H), 1.54-1.64 (broad m, 6H), 2.26-2.34 (m, 4H), 3.18-3.23 (m, 11H), 3.58-3.62 (m, 2H), 3.66 (s, 2H), 4.00-4.03 (m, 2H), 4.16-4.25 (m, 3H), 4.36-4.38 (m, 1H), 5.21-5.25 (m, 1H), 6.36-6.40 (d, 1H), 6.87-6.89 (t, 1H), 7.02-7.08 (m, 2H), 7.19-7.22 (d, 1H), 7.37-7.40 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.92 (s).

Chemical analysis: $C_{45}H_{72}N_3O_9PCl_2$. Calculated: C 60.00%, H 8.00%, N 4.66%, P 3.44%, Cl 7.88%. Found: C 59.64%, H 8.28%, N 4.69%, P 3.54%, Cl 7.66%.

1-Stearoyl-2-{6-[2'-(2",6"-dichloroanilino)phenylacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine.



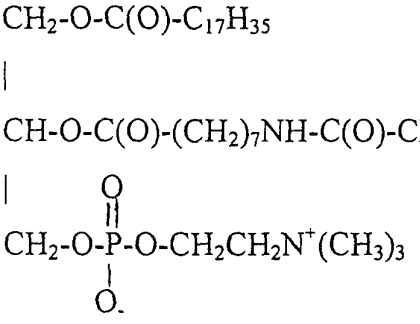
Yield 80%.

^{1}H NMR (CD_3OD), δ (ppm): 0.85-0.90 (t, 3H), 1.26-1.35 (broad s, 30H), 1.50-1.61 (m, 6H), 2.26-2.34 (m, 4H), 3.16-3.22 (m, 11H), 3.59-3.66 (m, 4H), 4.00-4.02 (m, 2H), 4.19-4.26 (several m, 3H), 4.38-4.40 (m, 1H), 5.21-5.25 (m, 1H), 6.37-6.40 (d, 1H), 6.83-6.90 (t, 1H), 6.99-7.07 (several m, 2H), 7.18-7.22 (d, 1H), 7.37-7.41 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.92 (s).

Chemical analysis: $C_{46}H_{74}N_3O_9PCl_2.2H_2O$. Calculated: C 58.10%, H 8.21%, N 4.42%, P 3.26%. Found: C 58.31%, H 8.36%, N 4.11%, P 3.30%.

1-Stearoyl-2-{8-[2'-(2",6"-dichloroanilino)phenylacetamido]octanoyl}-sn-glycero-3-phosphatidylcholine.



Yield 80%.

^{1}H NMR (CD_3OD), δ (ppm): 0.85-0.91 (t, 3H), 1.26-1.30 (broad s, 34H), 1.51-1.60 (m, 6H), 2.26-2.34 (m, 4H), 3.16-3.22 (m, 11H), 3.60-3.65 (m, 4H), 3.96-4.02 (m, 2H), 4.16-4.27 (several m, 3H), 4.38-4.40 (m, 1H), 5.19-5.24 (m, 1H), 6.36-6.40 (d, 1H), 6.83-6.90 (t, 1H), 6.99-7.09 (several m, 2H), 7.18-7.22 (d, 1H), 7.37-7.41 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.91 (s).

Chemical analysis: $C_{48}H_{78}N_3O_9PCl_2.2H_2O$. Calculated: C 58.90%, H 8.38%, N 4.29%, P 3.16%. Found: C 59.19%, H 8.39%, N 4.19%, P 3.20%.

EXAMPLE 2: Preparation of lipid derivatives of indomethacin (DP-Indo)

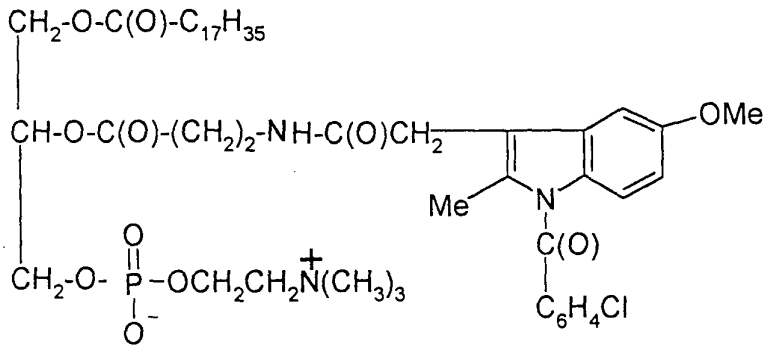
The procedure for the preparation of lipid derivatives of indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid) is the same as the process outlined in Example 1, steps 1 to 6, except that in step 6 instead of diclofenac the drug included in the reaction mixture is indomethacin.

Lipid derivatives of indomethacin (DP-Indo)

The synthesized compounds were subjected to TLC analysis under the following conditions: Silica gel 60 on aluminum sheet. Eluent is chloroform:methanol:water (65:35:5, v/v). Indicator is a spray of the

composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred at 100^0C.

1-Stearoyl-2-{3-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetamido]propanoyl}-sn- glycero-3-phosphatidylcholine.



Pale yellow wax. Yield 80%.

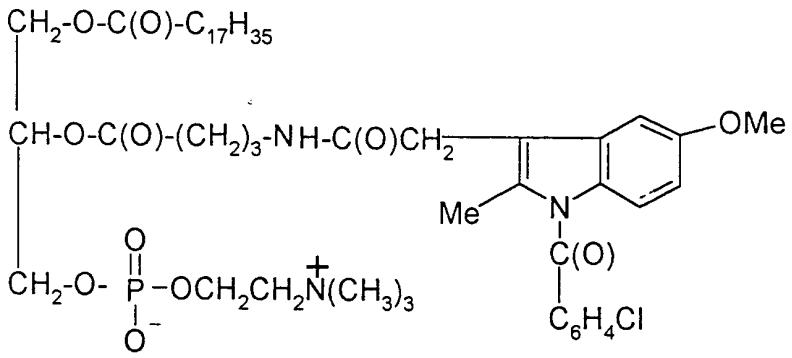
TLC analysis: One spot. R_f is 0.35.

^{1}H NMR (CD_3OD), δ (ppm): 0.85-0.91 (t, 3H), 1.26-1.30 (broad s, 28H), 1.52-1.55 (m, 2H), 2.25-2.31 (m, 5H), 2.54-2.60 (t, 2H), 3.18 (m, 9H), 3.43-3.46 (t, 2H), 3.57-3.62 (m, 4H), 3.81 (s, 3H), 3.98-4.02 (m, 2H), 4.13-4.25 (several m, 4H), 5.16 (m, 1H), 6.64-6.69 (d, 1H), 6.92-6.95 (d, 1H), 7.00 (s, 1H), 7.54-7.58 (d, 2H), 7.67-7.72 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.13 (s).

Chemical analysis: $C_{48}H_{73}N_3O_{11}PCl.2H_2O$. Calculated: C 59.41%, H 7.94%, N 4.33%, P 3.20%, Cl 3.66%. Found: C 59.79%, H 7.96%, N 3.91%, P 3.28%, Cl 3.60%.

1-Stearoyl-2-{4-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetamido]butanoyl}-sn- glycero-3-phosphatidylcholine.



Pale yellow wax. Yield 80%.

TLC analysis: One spot. R_f is 0.35.

^{1}H NMR (CD_3OD), δ (ppm): 0.85-0.91 (t, 3H), 1.26 (broad s, 28H), 1.52-1.55 (m, 2H), 1.77-1.83 (m, 2H), 2.24-2.39 (m, 7H), 3.18 (s, 9H), 3.21-3.29 (m, 2H), 3.57-3.60 (m, 4H), 3.80-3.81 (s, 3H), 3.98-4.01 (m, 2H), 4.15-4.36 (several m, 4H), 5.19-5.20 (m, 1H), 6.64-6.69 (d, 1H), 6.92-6.96 (d, 1H), 7.00 (s, 1H), 7.54-7.57 (d, 2H), 7.67-7.72 (d, 2H).

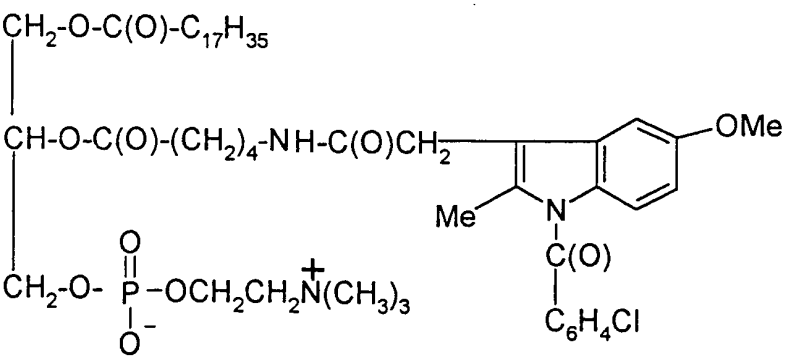
^{31}P NMR (CD_3OD), δ (ppm): -0.08 (s).

Chemical analysis: $C_{49}H_{75}N_3O_{11}PCl\ .H_2O$.

Calculated: C 60.90%, H 7.98%, N 4.27%, P 3.15%, Cl 3.67%.

Found: C 60.82%, H 8.35%, N 4.27%, P 3.10%, Cl 3.60%.

1-Stearoyl-2-{5-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetamido]valeroyl}-sn- glycero-3-phosphatidylcholine.



Pale yellow wax. Yield 80%.

TLC analysis: One spot. R_f is 0.35.

^{1}H NMR (CD_3OD), δ (ppm): 0.85-0.91 (t, 3H), 1.26 (s, 28H), 1.53-1.60 (m, 6H), 2.25-2.36 (m, 7H), 3.21 (s, 9H), 3.58-3.62 (m, 4H), 3.87-3.80 (s, 3H), 3.98-4.01 (m, 2H), 4.15-4.24 (several m, 3H), 4.35-4.37 (two d, 1H), 5.20-5.21 (m, 1H), 6.64-6.68 (d, 1H), 6.92-6.96 (d, 1H), 7.00 (s, 1H), 7.54-7.57 (d, 2H), 7.67-7.72 (d, 2H)

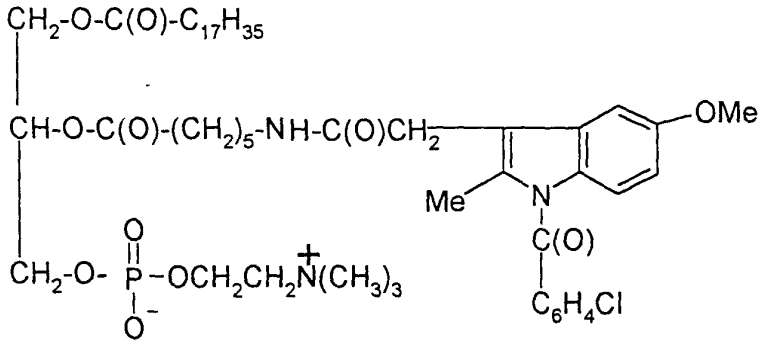
^{31}P NMR (CD_3OD), δ (ppm): -0.07(s).

Chemical analysis: $C_{50}H_{77}N_3O_{11}PCl \cdot 2H_2O$.

Calculated: C 60.15%, H 8.12%, N 4.21%, P 3.11%, Cl 3.56%.

Found: C 60.39%, H 8.33%, N 4.08%, P 3.05%, Cl 3.50%.

1-Stearoyl-2-{6-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetamido]hexanoyl}-sn- glycero-3-phosphatidylcholine.



Pale yellow wax. Yield 80%.

TLC analysis: One spot. R_f is 0.38.

^{1}H NMR (CD_3OD), δ (ppm): 0.85-0.91 (t, 3H), 1.26 (broad s, 30H), 1.48-1.62 (m, 6H), 2.26-2.32 (m, 7H), 3.15-3.19 (m, 11H), 3.59-3.62 (m, 4H), 3.80 (s, 3H), 3.96-4.01 (t, 2H), 4.16-4.25 (m, 3H), 4.36-4.38 (two d, 1H), 5.20-5.21 (m, 1H), 6.64-6.69 (d, 1H), 6.91-6.95 (d, 1H), 7.01 (s, 1H), 7.53-7.58 (d, 2H), 7.68-7.71 (d, 2H)

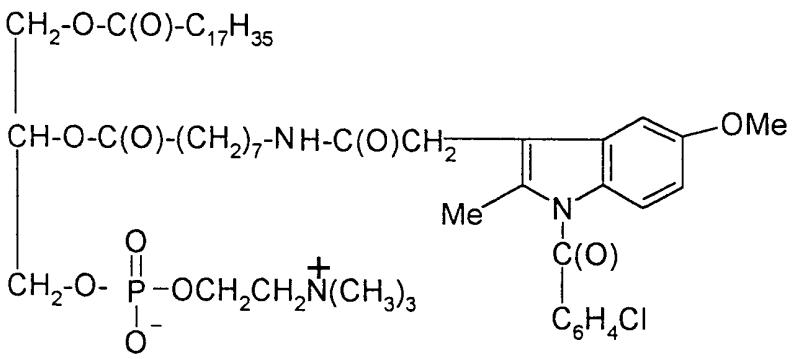
^{31}P NMR (CD_3OD), δ (ppm): -0.07(s).

Chemical analysis: $C_{51}H_{79}N_3O_{11}PCl \cdot H_2O$.

Calculated: C 61.60%, H 8.20%, N 4.22%, P 3.12%, Cl 3.57%.

Found: C 60.08%, H 8.35%, N 4.27%, P 3.22%, Cl 3.60%.

1-Stearoyl-2-{8-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetamido]octanoyl}-sn- glycero-3-phosphatidylcholine.



Pale yellow wax. Yield 80%.

TLC analysis: One spot. R_f is 0.38.

^{1}H NMR (CD_3OD), δ (ppm): 0.85-0.91 (t, 3H), 1.26 (broad s, 34H), 1.51-1.57 (m, 6H), 2.26-2.33 (m, 7H), , 3.16-3.20 (m, 11H), 3.58-3.63 (m, 4H), 3.80 (s, 3H), 3.96-4.02 (t, 2H), 4.16-4.26 (m, 3H), 4.39-4.41 (two d, 1H), 5.21 (m, 1H), 6.64-6.69 (d, 1H), 6.91-6.95 (d, 1H), 7.01 (s, 1H), 7.53-7.58 (d, 2H), 7.68-7.71 (d, 2H)

^{31}P NMR (CD_3OD), δ (ppm): -0.08(s).

Chemical analysis: $C_{53}H_{83}N_3O_{11}PCl \cdot 2H_2O$.

Calculated: C 61.16%, H 8.46%, N 4.09%, P 3.03%, Cl 3.41%.

Found: C 61.21%, H 8.37%, N 4.04%, P 2.98%, Cl 3.47%.

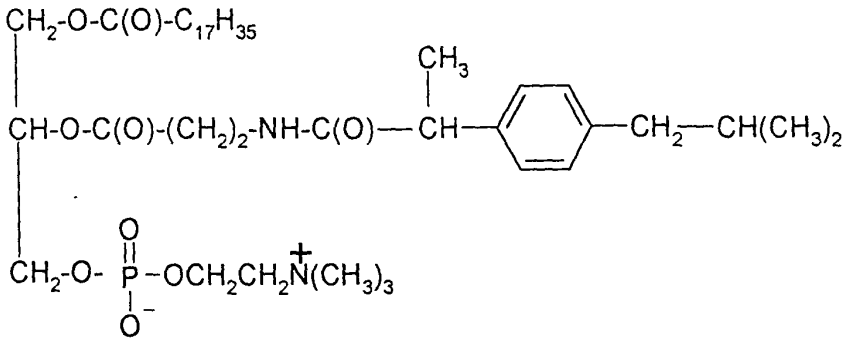
EXAMPLE 3: Preparation of lipid derivatives of ibuprofen (DP-Ibu)

The procedure for the preparation of lipid derivatives of ibuprofen (2-(4-isobutylphenyl)propionic acid) is the same as the process outlined in Example 1, steps 1 to 6, except that in step 6 instead of diclofenac the drug included in the reaction mixture is ibuprofen.

Lipid derivatives of ibuprofen (DP-Ibu)

The synthesized compounds were subjected to TLC analysis under the following conditions: Silica gel 60 on aluminum sheet. Eluent is chloroform:methanol:water (65:35:5, v/v). Indicator is a spray of the composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred at 100^0C.

1-Stearoyl-2-{3-[α-methyl-4-(2-methylpropyl)benzeneacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine.



White wax. Hygroscopic. Yield 60%.

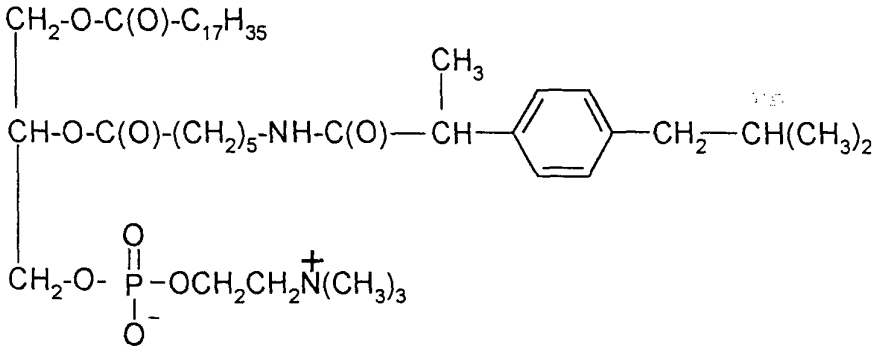
TLC analysis: One spot. R_f is 0.38.

^{1}H NMR (CD_3OD), δ (ppm): 0.88-0.93 (m, 9H), 1.29 (s, 28H), 1.41-1.44 (d, 3H), 1.58-1.63 (m, 2H), 1.80-1.90 (m, 1H), 2.28-2.35 (t, 2H), 2.43-2.46 (d, 2H), 2.51-2.57 (t, 2H), 3.22 (s, 9H), 3.40-3.45 (m, 2H), 3.61-3.66 (m, 3H), 3.98-4.41 (several m, 6H), 5.18 (m, 1H), 7.01-7.07 (d, 2H), 7.22-7.26 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.20(s).

Chemical analysis: $C_{42}H_{75}N_2O_9P$. $4H_2O$. Calculated: C 59.02%, H 9.93%, N 3.28%, P 3.63%. Found: C 59.26%, H 9.64%, N 3.43%, P 3.65%.

1-Stearoyl-2-{6-[α-methyl-4-(2-methylpropyl)benzeneacetamido]hexanoyl}-sn-glyce-ro-3-phosphatidylcholine.



White wax. Hygroscopic. Yield 50%.

TLC analysis: One spot. R_f is 0.38.

^{1}H NMR (CD_3OD), δ (ppm): 0.88-0.93 (m, 9H), 1.29 (broad s, 31H), 1.40-1.48 (m+d, 6H), 1.55-1.62 (m, 4H), 1.78-1.90 (m, 1H), 2.27-2.35 (m, 4H), 2.43-2.46 (d, 2H), 3.11-3.16 (m, 2H), 3.22 (s, 9H), 3.56-3.66 (m, 3H), 4.00-4.03 (t, 2H), 4.18-4.28 (several m, 4H), 5.18 (m, 1H), 7.07-7.11 (d, 2H), 7.22-7.25 (d, 2H).

^{31}P NMR (CD_3OD), δ (ppm): -0.20(s).

Chemical analysis: $C_{45}H_{81}N_2O_9P$. $2.5H_2O$. Calculated: C 62.07%, H 9.89%, N 3.22%, P 3.56%. Found: C 62.00%, H 10.01%, N 3.32%, P 3.19%.

EXAMPLE 4: Preparation of lipid derivatives of naproxen (DP-Nap)

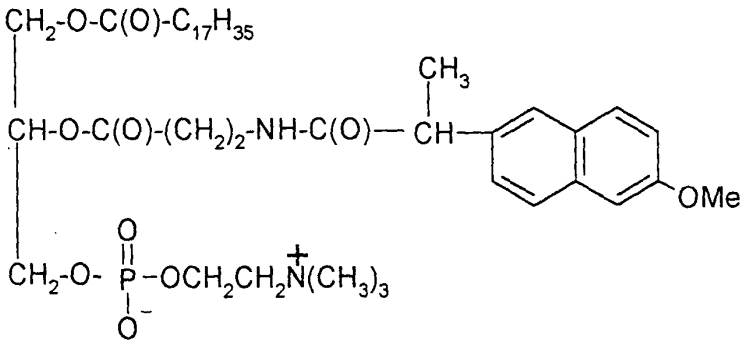
The procedure for the preparation of lipid derivatives of naproxen (d-2-(6-methoxy-2-naphthyl)pro-pionic acid) is the same as the process outlined in Example 1, steps 1 to 6, except that in step 6 instead of diclofenac the drug included in the reaction mixture is naproxen.

Lipid derivatives of naproxen (DP-Nap)

The synthesized compounds were subjected to TLC analysis under the following conditions: Silica gel 60 on aluminum sheet. Eluent is chloroform:methanol:water (65:35:5 v/v). Indicator is a spray of the

composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred at 100^0C.

1-Stearoyl-2-{3-[(S)-6-methoxy-α-methyl-2-naphtaleneacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine.



White wax. Hygroscopic. Yield 65%.

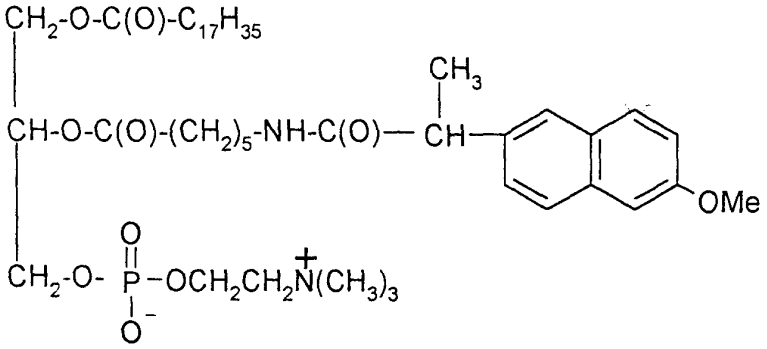
TLC analysis: One spot. R_f is 0.38.

^{1}H NMR (CD_3OD), δ (ppm): 0.86-0.91 (t, 3H), 1.26 (s, 28H), 1.50-1.53 (m, 5H), 2.23-2.29 (t, 2H), 2.51-2.57 (t, 2H), 3.16 (s, 9H), 3.41-3.46 (t, 2H), 3.56-3.60 (m, 2H), 3.78-3.80 (m, 1H), 3.88 (s, 3H), 3.97-4.02 (m, 2H), 4.12-4.31 (several m, 4H), 5.17-5.20 (m, 1H), 7.08-7.13 (d, 1H), 7.19 (s, 1H), 7.41-7.45 (d, 1H), 7.70-7.73 (m, 3H).

^{31}P NMR (CD_3OD), δ (ppm): -0.17(s).

Chemical analysis: $C_{43}H_{71}N_2O_{10}P$. $4H_2O$. Calculated: C 58.37%, H 8.93%, N 3.17%, P 3.50%. Found: C 58.34%, H 8.98%, N 3.25%, P 3.58%.

1-Stearoyl-2-{6-[(S)-6-methoxy-α-methyl-2-naphtaleneacetamido]hexanoyl}-sn-glycero-3-phosphatidyl



White wax. Hygroscopic. Yield 65%.

TLC analysis: One spot. R_f is 0.38.

^{1}H NMR (CD_3OD), δ (ppm): 0.87-0.91 (t, 3H), 1.26 (broad s, 32H), 1.44-1.57 (several m, 10H), 2.23-2.31(m, 4H), 3.14-3.20 (s, 9H), 3.60-3.62 (m, 2H), 3.75-3.78 (m, 1H), 3.88 (s, 3H), 4.00-4.02 (m, 2H), 4.17-4.38 (several m, 4H), 5.22 (m, 1H), 7.09-7.12 (d, 1H), 7.19 (s, 1H), 7.43-7.46 (d, 1H), 7.70-7.73 (m, 3H).

^{31}P NMR (CD_3OD), δ (ppm): -0.80(s).

Chemical analysis: $C_{46}H_{77}N_2O_{10}P$. $2H_2O$. Calculated: C 62.44%, H 9.16%, N 3.17%, P 3.50%. Found: C 62.73%, H 9.41%, N 3.29%, P 3.49%.

EXAMPLE 5: Solubility measurements of lipid derivatives of diclofenac, indomethacin, ibuprofen and naproxen

The solubility of several lipid derivatives of diclofenac, indomethacin, ibuprofen and naproxen was determined at room temperature (22°C) in aqueous solutions (water and saline) and in organic solutions (ethanol and octanol). In addition, the partition coefficient (P_c) values for these compounds, i.e their distribution ratios between the organic and the aqueous phases (octanol/saline), were calculated. The results, presented as the calculated $LogP_c$, are shown in Table 1.

The distribution of the compounds between the organic and the aqueous phases was measured by the shake-flask technique. Five milliliters of octanol containing about 3 mg of the studied compound were mixed with 5 ml saline. The mixture was shaken overnight at 22°C before the octanol and saline phases were separated. One ml from each phase was dissolved into an appropriate volume of ethanol so that the optical absorption of the obtained solution is in range of 0.1 to 1.0.

The coefficient P_c is calculated by the following ratio:

$$P_c = \frac{A_{oct} V_1 l_2}{A_{sal} V_2 l_1}$$

where A_{oct} is the optical absorption, at λ_{max}, of the ethanol solution in which one ml of octanol phase is dissolved, V_1 is the volume of this ethanol solution and l_1 is the width (cm) of the cuvette used for measurement of the optical absorption.

A_{sal} is the optical absorption, at λ_{max}, of the ethanol solution in which the one ml of saline phase is dissolved, V_2 is the volume of this ethanol solution and l_2 is the width (cm) of the cuvette used for measurement of the optical absorption.

Solubility values of the lipid derivatives of diclofenac, indomethacin, ibuprofen and naproxen in water and saline and their octanol/saline distributions are presented hereinbelow in table 1.

The tested lipid derivatives form suspensions or gel mixtures in water and saline. Solutions containing the lipid derivatives form suspensions or gel mixtures even after being filtrated through 0.45μm filter.

Table 1. Water and saline solubility and octanol/saline distribution coefficient (log P_c) of lipid derivatives at 22^0C.

Lipid derivatives have the structure: lyso-lecithin–linker–drug wherein the linker is -C(O)-(CH_2)n-NH-, the drug is diclofenac (DCF), indomethacin (Indo), ibuprofen (Ibu) or naproxen (Nap).

Lipid derivative		Solubility(mg/ml)		log P_c
Drug	n	Water	Saline	
DCF	2	0.003[a)]	0.002[a)]	2.8±0.1
DCF	3	0.002[a)]	0.002[a)]	≥3
DCF	4	0.002[a)]	0.002[a)]	≥3
DCF	5	0.0015[b)]	0.0015[b)]	≥3
DCF	7	0.001[b)]	0.001[b)]	≥3
Indo	2	less than 0.9[a)]	about 1.5[a)]	2.5
Indo	3	less than 0.6[a)]	about 1.5[a)]	2.5
Indo	4	less than 0.01[b)]	about 0.1[b)]	2.9
Indo	5	less than 0.01[b)]	about 0.01[b)]	3.2
Indo	7	about 0.005[b)]	-	3.7
Ibu	2	0.2[a)]	0.3[a)]	1.8
Ibu	5	0.5[a)]	0.5[a)]	≥3
Nap	2	0.01[a)]	0.06[a)]	≥3
Nap	5	0.2[a)]	0.2[a)]	≥3

[a)] Gel.

[b)] Suspension obtained after filtration through 0.45μm filter

The solubility measurements indicate that all the lipid derivatives examined dissolve well in ethanol and octanol, i.e more than 10 mg/ml at room temperature. The resulted solutions are transparent and the compounds remain stable in the solution for at least several days at room temperature.

It is evident that the lipid derivatives according to the invention have acquired the desired hydrophobic properties that are advantageous for brain penetration and sequestration.

EXAMPLE 6: In vitro cleavage of DP-DFC in tissue homogenates

The ability of the compounds of the invention to be cleaved to yield free diclofenac, was studied in vitro in homogenates of rat brain and liver. Two compounds were tested: the prodrug 1-Stearoyl-2-{4-[2'-(2",6"-dichloroanilino)-phenylacetamido]butanoyl}-sn-glycero-3-phosphatidylcholine (DP-DFC; Z=3), and the compound 1-Stearoyl-2-{3-[2'-(2",6"-dichloroanilino) -phenylacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine (DP-DFC; Z=2), comprising, respectively, a bridging group having a total of 4 and 3 carbon atoms.

Liver and brain were surgically removed, under pental anesthesia, from male Sabra rats weighing 250-280 g. About 1-1.5 g samples from each tissue were homogenized in PBS pH=7.4 (Dulbecco) at a ratio of 1:9 w/v of tissue to buffer.

DP-DFC was added to each homogenate to a final concentration of 40 μg/ml. The mixtures were incubated at 37°C in shaking for 1, 2, 3 and 6 hours, and then were placed on ice to stop the reaction.

The amounts of free diclofenac in 1 ml samples from either the brain or liver homogenates were determined by reverse phase HPLC assay. The amount of protein in each sample was assayed by the Lowry method.

The amounts of free diclofenac released at each time point, calculated per 1 mg of protein, are shown in Table 2. The result for each time point represents the average of five repetitions using tissues from five individual animals.

Table 2: In vitro cleavage of DP-DFC

Time (hrs)	Free DFC (μg/mg protein)			
	DP-DFC; Z=3		DP-DFC; Z=2	
	brain	liver	brain	liver
0	0.05	0.07	N.D	N.D
1	0.36 ±0.08	0.18 ±0.09	N.D	N.D
2	0.65 ±0.06	0.23 ±0.05	N.D	N.D
3	0.75 ±0.15	0.33 ±0.14	N.D	N.D
6	1.30 ±0.40	0.45 ±0.14	N.D	N.D

N.D denotes undetectable amounts of free diclofenac.

As shown in Table 2, a significant cleavage of diclofenac from its lipid conjugate was demonstrated, both in the brain and liver homogenates, only for the prodrug DP-DFC; Z=3 and not for the compound DP-DFC; Z=2. These results assess the important role the bridging group plays in enabling the release of the drug from its phospholipid derivative.

Under the above-described experimental conditions, the amounts of diclofenac released from the prodrug in the brain and liver homogenates were equivalent, respectively, to 30 % and 15 % of the drug introduced as DP-DFC.

In order to evaluate the effect of temperature on the reaction, a parallel set of incubations was carried out at 4°C. It was found that cooling to 4°C completely inhibited the cleavage of DP-DFC; Z=3 to DFC (data not shown).

The time and temperature dependent manner of the diclofenac release in the homogenates supports the conclusion that the drug is enzymatically cleaved from the prodrug molecule.

EXAMPLE 7: In vivo penetration of diclofenac into rat brain after i.v. injection of DP-DFC

The time-dependent penetration of lipid conjugates of diclofenac is measured in rat serum and brain after i.v. administration of DP-DFC.

10 mg/kg of DP-DFC are intravenously injected to male Sabra rats weighing 250-280 g. The prodrug (5 mg/ml) is formulated as follows: 50 mg DP-DFC are dissolved in 300-400 µl ethanol, and Lipofundin® (B. Braun, Melsungen, Germany) is added upto a final volume of 10 ml. The amount of the formulated prodrug injected to the animals is 2 ml/kg body weight.

The animals are sacrificed 0.5, 1, 2 and 3 hours following injection. Whole brain and blood samples are obtained from individual rats for each time point. The serum is separated by centrifugation of the blood (5 min. at about 800X g). The brain is treated as follows: whole brain is homogenized in saline. Half of the homogenate is extracted into organic solvents (methanol-chloroform 1:2) and is used for determination the level of the lipid derivative (DP-DFC). The other half is acidified by 85% H_3PO_4, extracted into chloroform and is used for determination of the level of free diclofenac (DFC). Each of the organic phases is separated by centrifugation, dried over Na_2SO_4 and evaporated. The obtained residues are dissolved in the corresponding mobile phase used in the HPLC method, and the amounts of both DP-DFC and DFC are determined by reverse phase HPLC.

Conclusion: Following i.v. administration of the prodrug, DP-DFC penetrates the blood-brain barrier (BBB) and is released in the brain tissue.

EXAMPLE 8: In vivo efficacy study of DP-DFC

Efficacy of DP-DFC lipid derivatives is tested in vivo in the model system of mouse carrageenan edema test.

Carrageenan-induced mouse paw edema is a widely employed animal model for acute inflammation. The objective of the study is to assess the potential prophylactic effects of DP-DCF derivatives on the prevention of inflammatory swelling and, in particular, to compare the efficacy parameters

with those obtained for diclofenac. The experimental set-up is as follows: Male Balb/c or CD-1 mice weighing 19-23g are observed for at least three days for signs of ill health, prior to initiation of the study. The animals, six per group, are i.p. injected with DP-DFC at a dose of 30mg/kg two, four and six hours prior to the induction of inflammation with carrageenan. Animals injected with the vehicle without prodrug serve as the control group.

Paw edema is induced by a single sub-plantar injection of 30µl of 2% carrageenan in physiological saline, into test animals' right hind paws. Just prior to paw edema induction, the mice are subject to light anesthesia by CO_2 and the paw thickness of their right hind paws is measured in triplicate using a plethysmograph and micrometer to provide a baseline. Four hours post carrageenan injection, the right paw thickness is measured in the same manner as before.

The assessment of potential anti-inflammatory activity is based on the relative reduction (%) in mean group values of carrageenan-induced right hind paw edema in tests article treated groups versus respective values in the vehicle control group.

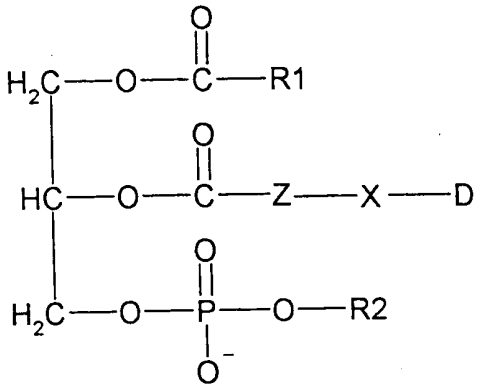
The effect of DP-DCF on Carrageenan Induced Paw Edema is also compared to diclofenac by following two criteria: a) severity of inflammation as determined by hind paw swelling, and b) expressed clinical signs as a measure for toxicity in reaction to treatment

Pilot studies of this kind indicate that the phospholipid derivatives of diclofenac have improved efficacy and toxicity compared to diclofenac in the carrageenan-induced paw edema model for inflammation.

While the present invention has been particularly described, persons skilled in the art will appreciate that many variations and modifications can be made. Therefore, the invention is not to be construed as restricted to the particularly described embodiments, rather the scope, spirit and concept of the invention will be more readily understood by reference to the claims which follow.

CLAIMS:

1. A compound of the general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R1 is a saturated or unsaturated, substituted or unsubstituted hydrocarbon chain having from 2 to 30 carbon atoms;

R2 is H or a phospholipid head group;

D is the residue of a nonsteroidal anti-inflammatory drug having a functional group selected from the group consisting of carboxyl, hydroxyl, amine and thiol, wherein D is attached through said functional group to a bridging group, -C(O)-Z-X- , wherein Z is a saturated or unsaturated hydrocarbon chain having from 2 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups, such that when the functional group of D is carboxyl, X is selected from amino, hydroxy and thio, and when the functional group of D is amino, hydroxy or thio, X is a carbonyl group.

2. The compound according to claim 1, wherein the drug derivative is inactive.

3. The compound according to claim 1, wherein an ester bond at position sn-2 of the phospholipid of the general formula I is cleaveable by a lipase.

4. The compound according to claim 3, wherein said lipase is a phospholipase.

5. The compound according to claim 4, wherein said phospholipase is phospholipase A_2 (PLA_2).

6. The compound according to claim 1, wherein R1 is an hydrocarbon chain having from 10 to 20 carbon atoms.

7. The compound according to claim 1, wherein R1 is an hydrocarbon chain having 15 or 17 carbon atoms.

8. The compound according to claim 1, wherein D is selected from the group consisting of diclofenac, indomethacin, ibuprofen and naproxen.

9. The compound according to claim 1, wherein R2 is selected from the group consisting of choline, ethanolamine, inositol and serine.

10. The compound according to claim 1 selected from the group consisting of:

1-Stearoyl-2-{3-[2'-(2",6"-dichloroanilino)phenylacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{4-[2'-(2",6"-dichloroanilino)phenylacetamido]butanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{5-[2'-(2",6"-dichloroanilino)phenylacetamido]valeroyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[2'-(2",6"-dichloroanilino)phenylacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{8-[2'-(2",6"-dichloroanilino)phenylacetamido]octanoyl}-sn-glycero-3-phosphatidylcholine'

1-Stearoyl-2-{3-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]propanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{4-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]butanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{5-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]valeroyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{8-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]octanoyl}-sn-glycero-3-phosphatidylcholine,

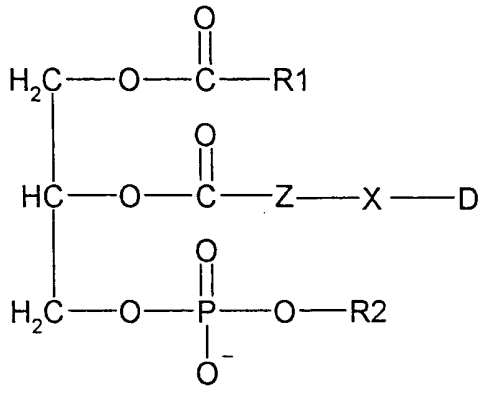
1-Stearoyl-2-{3-[α-methyl-4-(2-methylpropyl)benzeneacetamido] propanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[α-methyl-4-(2-methylpropyl)benzeneacetamido] hexanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{3-[(S)-6-methoxy-α-methyl-2-naphtaleneacetamido] propanoyl}-sn-glycero-3-phosphatidylcholine, and

1-Stearoyl-2-{6-[(S)-6-methoxy-α-methyl-2-naphtaleneacetamido] hexanoyl}-sn-glycero-3-phosphatidylcholine.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as an active ingredient, a compound of the general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R1 is a saturated or unsaturated, substituted or unsubstituted hydrocarbon chain having from 2 to 30 carbon atoms;

R2 is H or a phospholipid head group;

D is the residue of a nonsteroidal anti-inflammatory drug having a functional group selected from the group consisting of carboxyl, hydroxyl, amine and thiol, wherein D is attached through said functional group to a bridging group, -C(O)-Z-X- , wherein Z is a saturated or unsaturated hydrocarbon chain having from 3 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups, such that when the functional group of D is carboxyl, X is selected from amino, hydroxy and thio, and when the functional group of D is amino, hydroxy or thio, X is a carbonyl group.

12. The pharmaceutical composition according to claim 11, wherein -C(O)-Z-X-D is an inactive drug derivative.

13. The pharmaceutical composition according to claim 11, wherein an ester bond at position sn-2 of the phospholipid of the general formula I is cleaveable by a lipase.

14. The pharmaceutical composition according to claim 13, wherein said lipase is a phospholipase.

15. The pharmaceutical composition according to claim 14, wherein said phospholipase is phospholipase A_2 (PLA_2).

16. The pharmaceutical composition according to claim 11, wherein R1 is an hydrocarbon chain having from 10 to 20 carbon atoms.

17. The pharmaceutical composition according to claim 11, wherein R1 is an hydrocarbon chain having 15 or 17 carbon atoms.

18. The pharmaceutical composition according to claim 11, wherein D is selected from the group consisting of diclofenac, indomethacin, ibuprofen and naproxen.

19. The pharmaceutical composition according to claim 11, wherein R2 is selected from the group consisting of choline, ethanolamine, inositol and serine.

20. The pharmaceutical composition according to claim 11, wherein said compound of the general formula I is selected from the group consisting of:

1-Stearoyl-2-{4-[2'-(2",6"-dichloroanilino)phenylacetamido]butanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{5-[2'-(2",6"-dichloroanilino)phenylacetamido]valeroyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[2'-(2",6"-dichloroanilino)phenylacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{8-[2'-(2",6"-dichloroanilino)phenylacetamido]octanoyl}-sn-glycero-3-phosphatidylcholine'

1-Stearoyl-2-{4-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]butanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{5-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]valeroyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]hexanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{8-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl indolylacetamido]octanoyl}-sn-glycero-3-phosphatidylcholine,

1-Stearoyl-2-{6-[α-methyl-4-(2-methylpropyl)benzeneacetamido] hexanoyl}-sn-glycero-3-phosphatidylcholine, and

1-Stearoyl-2-{6-[(S)-6-methoxy-α-methyl-2-naphtaleneacetamido] hexanoyl}-sn-glycero-3-phosphatidylcholine.

21. The pharmaceutical composition according to any one of claims 11 to 20, in the form of solutions, suspensions, capsules, tablets, aerosols, gels, ointments or suppositories.

22. The pharmaceutical composition according to any one of claims 11 to 20 for oral, ocular, nasal, parenteral, topical or rectal administration.

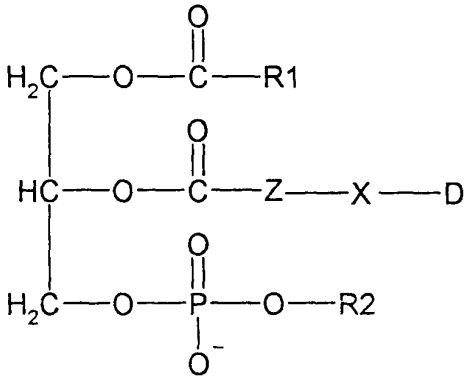
23. The pharmaceutical composition according to claim 22 for oral administration.

24. The pharmaceutical composition according to claim 22 for nasal administration.

25. The pharmaceutical composition according to any one of claims 11 to 24 for the treatment of a disease or disorder related to an inflammatory condition.

26. The pharmaceutical composition according to claim 25, wherein said disease or disorder related to an inflammatory condition is selected from the group consisting of arthritis, rheumatoid arthritis, asthma, psoriasis, systemic lupus erythematosus, inflammatory bowel syndrome and the neurological diseases and disorders multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, vascular dementia, epilepsy, migraines, stroke and trauma.

27. Use of a compound of the general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R1 is a saturated or unsaturated, substituted or unsubstituted hydrocarbon chain having from 2 to 30 carbon atoms;

R2 is H or a phospholipid head group;

D is the residue of a nonsteroidal anti-inflammatory drug having a functional group selected from the group consisting of carboxyl, hydroxyl, amine and thiol, wherein D is attached through said functional group to a bridging group, -C(O)-Z-X- , wherein Z is a saturated or unsaturated hydrocarbon chain having from 3 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups, such that when the functional group of D is carboxyl, X is selected from amino, hydroxy and thio, and when the functional group of D is

amino, hydroxy or thio, X is a carbonyl group,
for the preparation of a pharmaceutical composition substantially as described in the specification.

28. A method for treatment of a disease or disorder related to an inflammatory condition comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition according to any one of claims 11 to 26.

29. The method according to claim 28, wherein said disease or disorder related to an inflammatory condition is selected from the group consisting of arthritis, rheumatoid arthritis, asthma, psoriasis, systemic lupus erythematosus, inflammatory bowel syndrome and the neurological diseases and disorders multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, vascular dementia, epilepsy, migraines, stroke and trauma.

30. A process for the synthesis of compounds of the general formula I as defined in claim 1, comprising:

(i) providing a molecule y-X-Z-COOH, wherein y is selected from H and OH, Z is a saturated or unsaturated hydrocarbon chain having from 2 to 15 carbon atoms, and X is selected from amino, hydroxy, thio and carbonyl groups;

(ii) replacing y with an appropriate blocking group, B;

(iii) preparing an anhydride of the molecule B-X-Z-COOH;

(iv) acylating a lyso-lecithin by the anhydride of step (iii) to yield 1-acyl-2-acyl(X-B)-sn-glycero-3 phospholipid;

(v) removing the blocking group B from the functional group X; and

(vi) coupling a nonsteroidal anti-inflammatory drug D to the functional group X,

thus, generating a molecule of the general Formula I.

31. The process according to claim 30 wherein the protected functional group X is -NH.

32. The process according to claim 30 wherein the phospholipid of step (vi) is phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol or phosphatidylserine.

33. The process according to claim 30 wherein the nonsteroidal anti-inflammatory drug D is selected from the group consisting of diclofenac, indomethacin, ibuprofen and naproxen.

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